

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of

Michel VAULTIER et al.

Conf. 4777

Application No. 10/529,361

Group 1793

Filed November 3, 2005

Examiner C. Koslow

COMPOSITIONS CONTAINING IONIC LIQUIDS  
AND THEIR USES, IN PARTICULAR IN ORGANIC SYNTHESIS

DECLARATION UNDER RULE 132

Assistant Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

I, Dr. Michel Vaultier, Director of Research at CNRS,  
declare as follows:

I am one of the inventors of the above-identified U.S.  
patent application. My relevant background and experience are set  
forth on the attached CV.

I have read the Official Action mailed September 13, 2007  
that rejects the claimed invention as being obvious over US patent  
application publication 2002/0010291, and I am familiar with the  
present application.

The compositions according to the claimed invention are  
different from those described in US patent application publication  
2002/0010291 applied in the Official Action because US'291 fails to  
disclose (1) a recyclable composition and (2) a soluble reaction  
support.

The claimed invention refers to a stable composition comprising an ionic liquid of formula  $A_2^+X_2^-$  providing a liquid matrix; and one functionalized salt of formula  $A_2^+X_2^-$  providing a soluble reaction support, said functionalized salt carrying one or more functions that allows the catching of molecules, functionalization of said molecules, and release of said functionalized molecules after a reaction sequence so that the composition is recyclable, and said functionalized salt being dissolved in the liquid matrix so that the composition forms a homogeneous phase, which is not anticipated by US'291.

US'291 relates to a process for forming polyisobutylenes, employing an ionic liquid. Ionic liquids are used as initiators or as co-solvents in the polymerization reaction.

In paragraph[0053] of US'291, an ionic liquid containing a functional group:

- that can act as a catalyst or scavenger, or,
- that can bind to a catalyst or a scavenger

is described.

In paragraph [0054], a mixture of the ionic liquid containing a functional group and a non-functionalized ionic liquid is used to form a useful catalyst composition.

US'291 does not disclose that it is possible to recycle the functionalized ionic liquid after having bound either the catalyst or the scavenger to it. Recyclability is neither described nor suggested.

Thus, the functionalized ionic liquid described in US'291

is not a soluble reaction support. The scavenger or the catalyst bound to the functionalized ionic liquid is not subsequently functionalized, and is not released at the end of the reaction.

In conclusion, the compositions of claims 114-124 are novel over US patent application 2002/0010291.

Moreover, on the one hand, the aim of using a catalyst is not to functionalize it, but to use it to achieve a chemical reaction on another molecule. The catalyst is recovered (when recyclable) at the end of the chemical reaction in its initial state, and is not further functionalized. Thus, there is no motivation, teaching or suggestion for the man skilled in the art to use neither the functionalized ionic liquid of US'291, nor the catalyst of US'291 bound to the functionalized ionic liquid, as a soluble reaction support.

On the other hand, the aim of using a scavenger is to capture any excess of starting material which did not react, or any undesirable by-product which was formed during the chemical reaction. Then the scavenger is eliminated from the reaction mixture, without further functionalization. Accordingly, a scavenger is used as a purification method, but not as a soluble reaction support. Thus, there is no motivation, teaching or suggestion for the man skilled in the art to use neither the functionalized ionic liquid of US'291, nor the scavenger bound to the functionalized ionic liquid of US'291, as a soluble reaction support.

To conclude, US'291 does not teach nor suggest a soluble reaction support, and the uses disclosed by US'291 for the functionalized ionic liquid, i.e., to bind to a catalyst or a scavenger, do not motivate the man skilled in the art to use it as a soluble reaction support.

In conclusion, the compositions of claims 114-124 involve an inventive step in regard to US patent application 2002/0010291.

The following peer-reviewed publications refer to the claimed invention as a major breakthrough, and are provided along with this declaration as evidence that the claimed invention satisfies a long-felt need:

- M. Vaultier, V. Singh, A. Kirschning, chapter 5 in "Ionic Liquids in Synthesis" 2<sup>nd</sup> Edit., Wasserscheid, Peter / Welton, Thomas, 2007, 724p., ISBN-10:3-527-31239-0, Wiley-VCH, Weinheim.

Chapter 5.5. discloses task specific ionic liquids as new phases for supported organic synthesis. Page 489, lines 34-36, teaches that *"The idea of specifically designing either simple TSILs(Task Specific Ionic Liquids) or BTSILs (Binary Task Specific Ionic Liquids) in order to use them as phases for SPOS(Supported Organic Synthesis) arose in the groups of Bazureau[17] and Vaultier [18, i.e., the present invention] in early 2000."*



- Dubois, Philippe; Marchand, Gilles; Fouillet, Yves; Berthier, Jean; Douki, Thierry; Hassine, Fatima; Gmouh, Said; Vaultier, Michel. *Analytical Chemistry* (2006), 78(14), 4909-4917.

The end of column 3 page 4910 teaches that "*Moreover, TSILs(Task Specific Ionic Liquids)and RTILs (Room Temperature Ionic Liquids) can be combined in solutions. Hence, supported synthesis in a homogeneous solution can be achieved, which is a major advantage.[28, i.e., the present invention, 29]"*

- Ouach A. et al. *Tetrahedron* (2008), doi: 10.1016/j.tet.2007.11.060, article in press.

Column 1 teaches that "*Recently was developed synthesis, the Onium Salt Supported Organic Synthesis(OSSOS).[1 i.e., present invention,2]"*

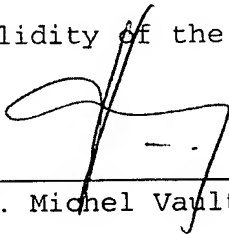
- Verron, Julien; Joerger, Jean-Michel; Pucheault, Mathieu; Vaultier, Michel. *Tetrahedron Letters* (2007), 48(23), 4055-4058.

Page 4055 teaches "*In addition, we [7, i.e., the present invention], then others [8] thought to use functionalized onium salts(...) as soluble supports for organic synthesis (...). This basically led to the new concept of onium salts supported organic synthesis."*

Application No. 10/529,361

Docket No. 0508-1131

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

  
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Dr. Michel Vaultier

Date \_09/01/2008\_\_\_\_\_

CURRICULUM VITAE:

VAULTIER Michel,

Birth date: 03/30/ 1946

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DIPLOMA :

Master of Sciences (1971), University of Rennes 1.

Doctorat of speciality (1973), University of Rennes 1.

PhD: 1977, University of Rennes 1. (Adviser: Pr R.Carrié, Title: reactivity of azomethine ylides with electrophilic and nucleophilic reagents )

POST-DOCTORAL STAY:

- University of Wisconsin (Madison), U.S.A., laboratory of Pr. B.M. Trost (1978 - 1979). Sulfur chemistry.

CURRENT POSITION AT C.N.R.S:

- Director of Research

RESPONSABILITIES (PAST AND PRESENT):

- Head of CNRS team N° 6510 « Organic Synthesis and electrosynthesis (1996- 2005).
- Director of the Chemistry Institute of RENNES (01/01/2005→ 12/31/2005...)
- Member of National Comity for Scientific Research (1995→2004).
- Member of the Scientific Council of the University of Rennes1 (1994-1999)
- Vice-President of the organic division of the French Chemical Society (2002 →2006)

- President of the organic division of the French Chemical Society (2007- )

- Head of a research group in UMR 6510 (10 PhD's and post-docs)

#### TEACHING:

##### Master2 degree:

- strategies for multistep synthesis,
- organometallics in organic synthesis,

#### CONSULTING :

- CNRS
- ORIL Industries
- Aventis
- Rhodia

#### SCIENTIFIC ACTIVITIES

- 179 publications in international Journals.
- 3 book chapters
- 15 world patents, 4 under national phases, one licensed.
- More than 100 conferences and seminars
- 45 PhD thesis completed.
- More than 100 short stay students (3-6 months)
- 22 post-doctoral stays.

#### THEMATIC OF RESEARCH:

- General: organic synthesis
- 1982-1992: Azide chemistry and aminoalkylation methodologies
- 1987 → 1998: polyamine chemistry and biology (cancer research)
- 1990 → 2004: chemistry of ceramic precursors (BN, BNSiX (X= P, Ge, Sn, Ti, Zr...)). Carbon composites.
- 1985 → Boron chemistry for organic synthesis
- 1998 → Sustainable chemistry: chemistry in and of ionic liquids (organometallics, bio-catalysis, organic synthesis, catalysis, multicyclic systems.)
- 2000 → ...Design and applications of Task specific ionic liquids:
  - New soluble supports
  - Applications to combinatorial chemistry
  - Droplets microreactors
  - High throughput synthesis
  - Functionalized composites

Author Name task started on Mon Jun 4, 2007 at 4:26 PM

Explored by Author in CAPLUS and MEDLINE.

Vaultier, m

Selected 2 of 3 candidates

VAULTIER M (46 references)

VAULTIER MICHEL (156 references)

179 references were found (23 duplicates removed)

First 100 are given

**Copper(I)-catalyzed [2+2] photocycloaddition of nonconjugated alkenes in room-temperature ionic liquids.** Malik, Chanchal K.; Vaultier, Michel; Ghosh, Subrata. Department of Organic Chemistry, Indian Association for the Cultivation of Science, Kolkata, India. *Synthesis* (2007), (8), 1247-1250.

**Task specific onium salts (TSOSs) as efficient soluble supports for Zard radical addition to olefins.** Verron, Julien; Joerger, Jean-Michel; Pucheault, Mathieu; Vaultier, Michel. UMR CNRS 6510, Campus de Beaulieu, Université de Rennes 1, Rennes, Fr. *Tetrahedron Letters* (2007), 48(23), 4055-4058.

**Toward green processes for fine chemicals synthesis: biocatalysis in ionic liquid-supercritical carbon dioxide biphasic systems.** Lozano, Pedro; De Diego, Teresa; Gmouh, Said; Vaultier, Michel; Iborra, Jose L. Departamento de Bioquímica y Biología Molecular B e Inmunología, Facultad de Química, Universidad de Murcia, Murcia, Spain. *ACS Symposium Series* (2007), 950(Ionic Liquids in Organic Synthesis), 209-223.

**On the importance of the supporting material for activity of immobilized *Candida antarctica* lipase B in ionic liquid/hexane and ionic liquid/supercritical carbon dioxide biphasic media.** Lozano, Pedro; De Diego, Teresa; Sauer, Tanja; Vaultier, Michel; Gmouh, Said; Iborra, Jose L. Departamento de Bioquímica y Biología Molecular B e Inmunología, Facultad de Química, Universidad de Murcia, Murcia, Spain. *Journal of Supercritical Fluids* (2007), 40(1), 93-100.

**Chemoenzymatic dynamic kinetic resolution of rac-1-phenylethanol in ionic liquids and ionic liquids/supercritical carbon dioxide systems.** Lozano, Pedro; Diego, Teresa; Larnicol, Mickael; Vaultier, Michel; Iborra, Jose L. Departamento de Bioquímica y Biología Molecular B e Inmunología, Facultad de Química, Universidad de Murcia, Murcia, Spain. *Biotechnology Letters* (2006), 28(19), 1559-1565.

**Peptide synthesis on onium salt-type soluble supports.** Vaultier, Michel; Roche, Celine; Gmouh, Said; Commercon, Alain. (Aventis Pharma SA, Fr.; Centre National De La Recherche Scientifique). Fr. Demande (2006), 67pp. CODEN: FRXXBL FR 2882057 A1 20060818 Patent written in French. Application: FR 2005-1557 20050216. Priority: . CAN 145:249518 AN 2006:820990

**Comparison and evaluation of two immobilisation techniques for task specific onium salts (TSOS) in Mizoroki-Heck cross coupling reactions.** Brochwitz, Christoph; Feldhoff, Armin; Kunz, Ulrich; Vaultier, Michel; Kirschning, Andreas. Institut fuer Organische Chemie, Universitaet Hannover, Hannover, Germany. *Letters in Organic Chemistry* (2006), 3(6), 442-446.

**Ionic Liquid Droplet as e-Microreactor.** Dubois, Philippe; Marchand, Gilles; Fouillet, Yves; Berthier, Jean; Douki, Thierry; Hassine, Fatima; Gmouh, Said; Vaultier, Michel. Department of Technology for Biology and Health, CEA/LETI, Grenoble, Fr. *Analytical Chemistry* (2006), 78(14), 4909-4917.

**[Ru(arene)(diamine)] catalysts in ionic liquids: recyclable catalytic systems for transfer hydrogenation.** Joerger, Jean-Michel; Paris, Jean-Marc; Vaultier, Michel. Institut de Chimie, UMR

CNRS 6510, University de Rennes 1, Rennes, Fr. ARKIVOC (Gainesville, FL, United States) (2006), (4), 152-160. Publisher: Arkat USA Inc., CODEN: AGFUAR [http://www.arkat-usa.org/ark/journal/2006/104\\_Lattes/1760/AL-1760FP%20as%20published%20mainmanuscript.pdf](http://www.arkat-usa.org/ark/journal/2006/104_Lattes/1760/AL-1760FP%20as%20published%20mainmanuscript.pdf)

**Droplet microreactor.** Marchand, Gilles; Vinet, Françoise; Delapierre, Guillaume; Hassine, Fatima; Gmouh, Said; Vaultier, Michel. (Commissariat à l'Energie Atomique, Fr.; Centre National de la Recherche Scientifique CNRS). Fr. Demande (2006), 63 pp. CODEN: FRXXBL FR 2872715 A1 20060113 Patent written in French. Application: FR 2004-7623 20040708. Priority: . CAN 144:130878 AN 2006:34549

**2-Pyridinealdoxime, a new ligand for a Pd-precatalyst: Application in solid-phase-assisted Suzuki-Miyaura reaction.** Solodenko, Wladimir; Brochwitz, Christoph; Wartchow, Rudolf; Hashem, Md. Abul; Dawood, Kamal M.; Vaultier, Michel; Kirschning, Andreas. Institut fuer Organische Chemie, Universitaet Hannover, Hannover, Germany. Molecular Diversity (2005), 9(4), 333-339.

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**Oxidative self-coupling of aromatic compounds in ionic liquids.** Mellah, M.; Zeitouny, J.; Gmouh, S.; Vaultier, M.; Jouikov, V. Laboratory of Molecular and Macromolecular Electrochemistry, UMR 6510, SESO, University of Rennes I, Campus de Beaulieu, Rennes, Fr. Electrochemistry Communications (2005), 7(9), 869-874.

**Antioxidative properties of natural polyamines and dimethylsilane analogues.** Gaboriau, François; Vaultier, Michel; Moulinoux, Jacques-Philippe; Delcros, Jean-Guy. Inserm U522, CHRU Pontchaillou, Université de Rennes 1, Rennes, Fr. Redox Report (2005), 10(1), 9-18.

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**Stereospecific palladium-catalyzed borylation reaction of 1-alkenyl halides with diisopropylaminoborane.** Euzenat, Lisenn; Horhant, David; Brielles, Cedric; Alcaraz, Gilles; Vaultier, Michel. UMR CNRS 6510, Laboratoire SESO, Université de Rennes1, Rennes1, Fr. Journal of Organometallic Chemistry (2005), 690(11), 2721-2724.

**The influence of room-temperature ionic liquids on the stereoselectivity and kinetics of the electrochemical pinacol coupling of acetophenone.** Lagrost, Corinne; Hapiot, Philippe; Vaultier, Michel. Institut de Chimie de Rennes, UMR 6510 CNRS-Université de Rennes1, Rennes, Fr. Green Chemistry (2005), 7(6), 468-474.

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**Understanding Structure-Stability Relationships of Candida antarctica Lipase B in Ionic Liquids.** De Diego, Teresa; Lozano, Pedro; Gmouh, Said; Vaultier, Michel; Iborra, José L. Departamento de Bioquímica y Biología Molecular B e Inmunología, Facultad de Química, Universidad de Murcia, Murcia, Spain. Biomacromolecules (2005), 6(3), 1457-1464.

**Use of functionalized onium salts as a soluble support for organic synthesis, especially in ester**

**preparation.** Vaultier, Michel; Gmouh, Said; Hassine, Fatima. (Centre National de la Recherche Scientifique CNRS, Fr.; Université Rennes 1). Fr. Demande (2005), 190 pp. CODEN: FRXXBL FR 2857360 A1 20050114 Patent written in French. Application: FR 2003-8413 20030709. Priority: . CAN 142:134035 AN 2005:33164

**Fluorescence and CD spectroscopic analysis of the  $\alpha$ -chymotrypsin stabilization by the ionic liquid, 1-ethyl-3-methylimidazolium bis[(trifluoromethyl)sulfonyl]amide.** De Diego, Teresa; Lozano, Pedro; Gmouh, Said; Vaultier, Michel; Iborra, Jose L. Departamento de Bioquímica y Biología Molecular B e Inmunología, Facultad de Química, Universidad de Murcia, Murcia, Spain. Biotechnology and Bioengineering (2004), 88(7), 916-924.

**$^{11}\text{B}$  and  $^{15}\text{N}$  solid state NMR investigation of a boron nitride preceramic polymer prepared by ammonolysis of borazine.** Gervais, Christel; Framery, Eric; Duriez, Christophe; Maquet, Jocelyne; Vaultier, Michel; Babonneau, Florence. Laboratoire de Chimie de la Matière Condensée, UMR 7574, Université de Pierre et Marie Curie, Paris, Fr. Journal of the European Ceramic Society (2004), Volume Date 2005, 25(2-3), 129-135.

**Regioselective hydrosilylation of allylic derivatives by the siloxanes D4H and MDHM in the presence of platinum catalysts.** El Malki, A.; Hannioui, A.; Knouzi, N.; Vaultier, M.. Université Cadi Ayyad, FST Beni-Mellal, Beni-Mellal, Morocco. Physical & Chemical News (2004), 17(1), 107-112. Publisher: Best Edition, CODEN: PCNHBU ISSN: 1114-3800. Journal written in English. CAN 143:26659 AN 2004:782571

**One-step regioselective synthesis of 5-aminoisoxazoles from nitrile oxides and  $\alpha$ -cyanoenamides.** Saad, Amar; Vaultier, Michel; Derdour, Aiecha. Laboratoire de synthèse Organique Appliquée, Département de Chimie, Faculté des Sciences, Université d'Oran Es-sénia, Ouahrán, Algeria. Molecules (2004), 9(7), 527-534. Publisher: Molecular Diversity Preservation International, CODEN: MOLEFW ISSN: 1420-3049. <http://www.mdpi.net/molecules/papers/90700527.pdf> Journal; Online Computer File written in English. CAN 142:411270 AN 2004:718999

**The importance of complex stability for asymmetric copper-catalyzed cyclopropanations in [emim][OTf] ionic liquid: the bis(oxazoline)-azabis(oxazoline) case.** Fraile, Jose M.; Garcia, Jose I.; Herrerias, Clara I.; Mayoral, Jose A.; Reiser, Oliver; Vaultier, Michel. Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón, Facultad de Ciencias, Universidad de Zaragoza-CSIC, Zaragoza, Spain. Tetrahedron Letters (2004), 45(36), 6765-6768.

**Towards green processes for fine chemicals synthesis: Biocatalysis in ionic liquid/supercritical carbon dioxide biphasic systems.** Lozano, Pedro; De Diego, Teresa; Gmouh, Said; Vaultier, Michel; Iborra, Jose L. Departamento de Bioquímica y Biología Molecular "B" e Inmunología, Universidad de Murcia, E-30.100 Murcia, Spain. Abstracts of Papers, 228th ACS National Meeting, Philadelphia, PA, United States, August 22-26, 2004 (2004),

**Enantioselective catalytic asymmetric hydrogenation of ethyl acetoacetate in room temperature ionic liquids.** Berthod, Mikael; Joerger, Jean-Michel; Mignani, Gerard; Vaultier, Michel; Lemaire, Marc. UMR 5181, UCBL, CPE, Laboratoire de Catalyse et Synthèse Organique, Villeurbanne, Fr. Tetrahedron: Asymmetry (2004), 15(14), 2219-2221.

**Indium benzoates, and their use as catalysts of Friedel Crafts acylations, in particular benzoylations, of aromatic compounds.** Duquenne, Christophe; Vaultier, Michel; Gillet, Jean Philippe; Kervennal, Jacques; Ruppin, Christophe. (Atofina, Fr.). Fr. Demande (2004), 16 pp. CODEN: FRXXBL FR 2850104 A1 20040723 Patent written in French. Application: FR 2003-674 20030122. Priority: . CAN 141:140182 AN 2004:591906

**Process for preparation of ketones, especially benzophenone, by Friedel-Crafts acylation, in particular benzoylation, of aromatic compounds in the presence of  $\text{In}_2\text{O}_3$  or  $\text{In}(\text{OH})_3$  as recyclable**

**catalysts.** Duquenne, Christophe; Vaultier, Michel; Gillet, Jean Philippe. (Atofina, Fr.). Fr. Demande (2004), 16 pp. CODEN: FRXXBL FR 2850102 A1 20040723 Patent written in French. Application: FR 2003-675 20030122. Priority: . CAN 141:140181 AN 2004:591905

**Specific Effects of Room Temperature Ionic Liquids on Cleavage Reactivity: Example of the Carbon-Halogen Bond Breaking in Aromatic Radical Anions.** Lagrost, Corinne; Gmouh, Said; Vaultier, Michel; Hapiot, Philippe. *Synthese et Electrosynthese Organiques*, UMR CNRS No. 6510, Institut de Chimie de Rennes, Université de Rennes 1, Rennes, Fr. *Journal of Physical Chemistry A* (2004), 108(29), 6175-6182.

**Preparation of an advanced phenylglycine-derived intermediate en route to the southern hemisphere tetraene of viridenomycin.** Maw, Graham N.; Thirsk, Carl; Toujas, Jean-Louis; Vaultier, Michel; Whiting, Andrew. Pfizer Global Research and Development, Sandwich, UK. *Synlett* (2004), (7), 1183-1186.

**Synthesis of glycidyl esters catalyzed by lipases in ionic liquids and supercritical carbon dioxide.** Lozano, Pedro; De Diego, Teresa; Carrie, Daniel; Vaultier, Michel; Iborra, Jose L. Facultad de Química, Departamento de Bioquímica y Biología Molecular B e Inmunología, Universidad de Murcia, Murcia, Spain. *Journal of Molecular Catalysis A: Chemical* (2004), 214(1), 113-119.

**Compositions containing ionic liquids and functionalized salts and their use as liquid matrixes and reaction supports in organic synthesis, especially in ester preparation.** Vaultier, Michel; Gmouh, Said. (Centre National de la Recherche Scientifique Cnrs, Fr.; Université Rennes 1). Fr. Demande (2004), 129 pp. CODEN: FRXXBL FR 2845084 A1 20040402 Patent written in French. Application: FR 2002-11910 20020926. Priority: . CAN 140:303091 AN 2004:271185

**Superoxide-stable ionic liquids: new and efficient media for electrosynthesis of functional siloxanes.** Martiz, Bruno; Keyrouz, Robert; Gmouh, Said; Vaultier, Michel; Jouikov, Viatcheslav. Departamento de Química Orgánica, Facultad de Química, Universidad de Murcia, Murcia, Spain. *Chemical Communications (Cambridge, United Kingdom)* (2004), (6), 674-675.

**Criteria to Design Green Enzymatic Processes in Ionic Liquid/Supercritical Carbon Dioxide Systems.** Lozano, Pedro; de Diego, Teresa; Gmouh, Said; Vaultier, Michel; Iborra, Jose L. Departamento de Bioquímica y Biología Molecular B e Inmunología Facultad de Química, Universidad de Murcia, Murcia, Spain. *Biotechnology Progress* (2004), 20(3), 661-669.

**Kinetic resolution of rac-2-pentanol catalyzed by *Candida antarctica* lipase B in the ionic liquid, 1-butyl-3-methylimidazolium bis[(trifluoromethyl)sulfonyl]amide.** Noel, Marilyne; Lozano, Pedro; Vaultier, Michel; Iborra, Jose L. Facultad de Química, Departamento de Bioquímica y Biología Molecular B e Inmunología, Universidad de Murcia, Murcia, Spain. *Biotechnology Letters* (2004), 26(4), 301-306.

**Comparison of the immobilization of chiral bis(oxazoline)-copper complexes onto anionic solids and in ionic liquids.** Fraile, Jose M.; Garcia, Jose I.; Herrerias, Clara I.; Mayoral, Jose A.; Gmouh, Said; Vaultier, Michel. Facultad de Ciencias, Instituto de Ciencia de Materiales de Aragón, Departamento de Química Orgánica, Universidad de Zaragoza-C.S.I.C., Zaragoza, Spain. *Green Chemistry* (2004), 6(2), 93-98. Publisher: Royal Society of Chemistry, CODEN: GRCHFJ ISSN: 1463-9262. Journal written in English. CAN 141:313899 AN 2004:79080

**Rhodium catalyzed coupling reaction of myrcene with ethyl acetoacetate in the ionic liquid 1-ethyl-3-methylimidazolium triflimide.** Dhanalakshmi, Kasi; Vaultier, Michel. Institut de Chimie, UMR CNRS 6510, SESO, Université de Rennes 1, Rennes, Fr. *Tetrahedron* (2003), 59(50), 9907-9911.

**Interaction of natural polyamines and dimethylsilyl analogues with a phospholipid monolayer: A**



**study by Brewster angle microscopy and PM-IRRAS.** Berdycheva, Olga; Desbat, Bernard; Vaultier, Michel; Saint-Pierre-Chazalet, Michele. Laboratoire de Physicochimie Biomoléculaire et Cellulaire, UMR CNRS 7033, Université Pierre et Marie Curie, Paris, Fr. Chemistry and Physics of Lipids (2003), 125(1), 1-11.

**Improved transparency- nonlinearity trade-off with boroxine-based octupolar molecules.** Alcaraz, Gilles; Euzenat, Lisenn; Mongin, Olivier; Katan, Claudine; Ledoux, Isabelle; Zyss, Joseph; Blanchard-Desce, Mireille; Vaultier, Michel. Synthèse et ElectroSynthèse Organiques (CNRS, UMR 6510), Institut de Chimie, Université de Rennes 1, Rennes, Fr. Chemical Communications (Cambridge, United Kingdom) (2003), (22), 2766-2767.

**Enzymatic catalysis in ionic liquids and supercritical carbon dioxide.** Lozano, Pedro; De Diego, Teresa; Carrie, Daniel; Vaultier, Michel; Iborra, Jose L. Departamento de Bioquímica y Biología Molecular B e Inmunología, Facultad de Química, Universidad de Murcia, Murcia, Spain. ACS Symposium Series (2003), 856(Ionic Liquids as Green Solvents), 239-250.

**Monomeric (dialkylamino)boranes: a new and efficient boron source in palladium catalyzed C-B bond formation with aryl halides.** Euzenat, Lisenn; Horhant, David; Ribourdouille, Yann; Duriez, Christophe; Alcaraz, Gilles; Vaultier, Michel. Université de Rennes1-Beaulieu, S. E. S. O. UMR-CNRS 6510, Rennes, Fr. Chemical Communications (Cambridge, United Kingdom) (2003), (18), 2280-2281.

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## 5

## Organic Synthesis

*Cinzia Chiappe, Martyn Earle, Frédéric Favre, Rasmus Fehrmann, A. Kirschning, Sven Kuhlmann, Hélène Olivier-Bourbigou, Anders Riisager, Peter Schulz, V. Singh, M. Vaultier, and Peter Wasserscheid*

## 5.1

## Ionic Liquids in Organic Synthesis: Effects on Rate and Selectivity

*Cinzia Chiappe*

## 5.1.1

## Introduction

An incredibly large number of papers have appeared in the last few years about organic reactions and catalyzed processes carried out in ionic liquids, demonstrating that these salts can be used with success as solvents for organic reactions. It has often been claimed that they are able to increase both the reactivity and/or selectivity of a number of processes [1]. Unfortunately, little is known about how the use of an ionic liquid can affect the reactivity of solute species.

Chemical reactivity in solution is determined by the ability of the solvent to interact with substrates, intermediates and transition states [2], as well as the intrinsic properties of the reacting solutes. With their unique properties, ionic liquids may induce solvent effects on a wide range of processes. For molecular solvents, the key properties determining the interactions are recorded as "polarity" and they can change the rate and the order of homogeneous chemical reactions, affect the contribution of competing processes, modify the stereochemical behavior and the product distribution. The ability of some ionic liquids to interact with solutes has been investigated [3] using both partition methods and solvatochromic dyes. Through these measurements, it has been shown that they are able to interact with solutes via dipolar and dispersion forces and act as strong hydrogen-bond acceptors. This latter property mainly depends on the anion, while the hydrogen-bond donor ability (when observed, the values of hydrogen-bond acidity depend on the method used for the

Table 5.1-1 Physicochemical properties and solvent parameters for several ionic liquids<sup>a</sup>.

	Viscosity (cP)	$\delta^2$ (J cm <sup>-3</sup> )	$E_T^N$	$\pi^*$	$\alpha$	$\beta$
[BMIM][BF <sub>4</sub> ]	233 (303 K)	998	0.67	1.047	0.627	0.376
[BMIM][PF <sub>6</sub> ]	450	912	0.669	1.032	0.634	0.207
[BMIM][SbF <sub>6</sub> ]		992		1.039	0.639	0.146
[BMIM][TfO]		620	0.656	1.006	0.625	0.464
[EMIM][Tf <sub>2</sub> N]	28					
[BMIM][Tf <sub>2</sub> N]	52	650	0.644	0.984	0.617	0.243
[BMMIM][BF <sub>4</sub> ] <sup>a</sup>			0.576	1.083	0.402	0.363
[BMPY][Tf <sub>2</sub> N]	85		0.544	0.954	0.427	0.252
[BMMIM][Tf <sub>2</sub> N]	97.1	586	0.541	1.010	0.381	0.239
[OMIM][PF <sub>6</sub> ]	682		0.633			
[OMIM][Tf <sub>2</sub> N]	92.7		0.629			
[OMMIM][Tf <sub>2</sub> N] <sup>a</sup>			0.525			
[OMMIM][BF <sub>4</sub> ]			0.543			

<sup>a</sup>[BMIM] = 1-butyl-3-methylimidazolium; [EMIM] = 1-ethyl-3-methylimidazolium; [OMIM] = 1-octyl-3-methylimidazolium; [BMMIM] = 1-butyl-2,3-dimethylimidazolium; [OMMIM] = 1-octyl-2,3-dimethylimidazolium; [BMPY] = 1-butyl-1-methylpyrrolidinium.

determination) arises from the cation. In particular, solvatochromic measurements have shown [3c] that all the investigated ionic liquids are characterized by dipolarities ( $\pi^*$ ) higher than those of most non-aqueous molecular solvents; depending on the anion they can have a significant hydrogen-bond basicity ( $\beta$ ) and, on the cation, a hydrogen-bond acidity ( $\alpha$ ) comparable to or lower than that of aniline, although this latter parameter is influenced also by the anion. No measure, however, suggests a "super polar" nature for the ionic liquids investigated (see Chapter 3, Section 3.5).

Ionic liquids have other physicochemical properties that can affect the reactivity of solute species; they are characterized by high viscosities, by elevated values of cohesive pressure and by a high degree of order. These properties are discussed in Chapter 3, but in Table 5.1-1 some physicochemical properties of several widely used ionic liquids are shown. The elevated viscosity may produce a reduction in the rate of diffusion-controlled processes, including the diffusion rates of redox species. The high cohesive pressure values, recently evaluated [4] on the basis of kinetic measurements (see below), show that more energy is necessary to create a hole in ionic liquids, whether to accommodate a solute or to bring all the components to the reaction site. Finally, the strong ion-ion interactions present in the ionic liquids lead to highly ordered three-dimensional supermolecular polymeric networks of anions and cations linked by hydrogen bonds [5] and/or Coulombic interactions [6], producing a completely different environment than found in molecular solvents. Higher energies are necessary to bring solutes together but the formation of the activated complex may be accompanied by a decrease in the order characterizing the overall system, with a consequent increase in the activation entropy.

Moreover, depending upon the cation and anion structure and size, the presence of polar and non-polar domains inside the liquid, which may affect the solvation



and diffusion of ions and neutral molecules, can arise [7]. The situation is made even more complicated by the addition of simple molecules, such as water, alcohols and aromatic compounds, which drastically modifies the three-dimensional structure of ionic liquids. In water at infinite dilution, ionic liquid components break away from their pure environment and settle in the water environment, probably as well-separated ions. As the concentration of the ionic liquid increases, its anions and cations begin to interact with each other, directly or mediated by H<sub>2</sub>O. At higher concentrations, ionic liquid ions cluster together with a very similar arrangement to that in the pure state [8, 9]. Water and small alcohols are hydrogen bonded strongly with the anion rather than the cation. Conversely, for non-hydrogen-bonding solutes, such as ethers and propane, the interaction is predominantly with the cation. Aromatic compounds (benzene, toluene and xylenes) form clathrate structures in 1-alkyl-3-methylimidazolium salts [10, 11].

The extent of mixing and the distribution of solutes in ionic liquids depend, therefore, on the relative solute–solute and solute–solvent interactions, which can have significant consequences on chemical reactivity and stability. In many ionic liquids, water-sensitive catalysts and chemical reactions are less sensitive to water compared with the situation in organic solvents because water dispersed throughout the ionic liquid cannot act like bulk water.

Finally, although, in general, molecular solvents affect the rates of homogeneous reactions via static or equilibrium solvent effects, dynamic or frictional solvent effects may be present in ionic liquids. The former are traditionally rationalized in terms of the transition-state theory; the solvent modifies the Gibbs energy of activation by differential solvation of the reactants and the activated complex. Here, it is necessary to assume that the required reorientational relaxation of the solvent molecules during the activation process is sufficiently fast and the activated complex is in thermal equilibrium with the solvent. For rapid reactions, in solvents characterized by slow solvation processes, this hypothesis is, however, not necessarily valid and the solvent may affect reaction rates through dynamic frictional effects. In the case of slow solvent relaxation, significant dynamic contributions to the experimentally determined activation parameters, which are completely absent in the conventional transition state theory, can exist and, in the extreme case, solvent reorientation can become the rate-limiting step: in this situation the rate depends on solvent dynamics and will vary with density, internal pressure and viscosity. In ionic liquids the strong anion–cation interactions affect the dynamic nature of solvation. Measured rotation times in ionic liquids are considerably slower than in polar molecular solvents [12, 13] suggesting that, while in polar solvents solvation arises due to the rearrangement of the solvent molecules around an instantaneously created dipole upon absorption of a photon, in ionic liquids the solvation is probably due to the motions of the ions.

It is evident from this brief introduction that ionic liquids may affect reactivity much more than molecular solvents. They are not only mixtures of two species interacting with each other (anion and cation), each able to give specific interactions with the dissolved reagents and/or activated complexes, but the anion–cation interactions make them complex three-dimensional structures able to exercise unusual effects.

This section attempts to show how ionic liquids are able to modify the kinetic and stereochemical course of organic reactions. It will cover, therefore, only a limited number of reactions and even a more limited number of ionic liquids, mainly those reported in Table 5.1-1. Unfortunately, only a few ionic liquids have been used in studies of reactivity and for even fewer are all of the physicochemical properties required to rationalize organic reactivity known. Sometimes, the data reported in the literature have been revised and reinterpreted in the light of more recent findings on the physicochemical properties of the applied ionic liquids. I express regret if I have misunderstood some results or some interpretations. My aim is merely to promote the discussion about ionic liquids' solvent properties in order to increase the understanding of these neoteric solvents and favor the development of more efficient processes.

### 5.1.2

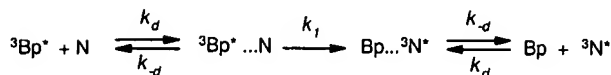
#### Ionic Liquid Effects on Reactions Proceeding through Isopolar and Radical Transition States

Traditionally, homogeneous organic reactions are grouped into three classes depending on the character of the activated complex through which the reactions proceed: dipolar, isopolar and free-radical transition state reactions. Reactions occurring through radical or isopolar transition states are generally unaffected, or only marginally affected, by solvent polarity. For these reactions other solvent properties such as cohesive pressure, viscosity and so on may become important.

##### 5.1.2.1 Energy Transfer, Hydrogen Transfer and Electron Transfer Reactions

Despite the fact that reactivity in ionic liquids has been only marginally investigated [1m] a relatively high number of quantitative studies have been carried out on reactions occurring through isopolar or radical transition states. By using a series of representative photochemical reactions, covering a wide range of fundamental processes (energy transfer, hydrogen transfer and electron transfer) it has been shown [14] that the slow molecular diffusion characterizing ionic liquids renders diffusion-controlled processes up to two orders of magnitude slower than in common organic solvents (e.g., acetonitrile, water). However, it is interesting to note that often the kinetic constants determined in ionic liquids for diffusion-controlled processes are at least an order of magnitude higher than the kinetic constants estimated from the ionic liquid's viscosity ( $k_{\text{diff}} = 8000 RT/3\eta$ ) [14b]. Related to this, the kinetic investigation of the exothermic energy transfer from benzophenone triplet ( $^3\text{Bp}^*$ ) to naphthalene (N) has shown that this phenomenon can be attributed to the very large solvent-dependent pre-exponential factors,  $A$ , characterizing the reaction in ionic liquids that overcompensate for the large  $E_a$  values (Scheme 5.1-1).

Moreover, both  $E_a$  and  $A$  values show a significant dependence on the ionic liquid structure. For any cation the  $E_a$  values are 12–15 kJ mol<sup>-1</sup> higher for the  $[\text{PF}_6]^-$  salts than the  $[\text{Tf}_2\text{N}]^-$  and this behavior has been related to the higher extent of ionic cross-linking characterizing the ionic liquids bearing the smaller and more



**Scheme 5.1-1** Exothermic energy transfer from benzophenone triplet ( ${}^3\text{Bp}^*$ ) to naphthalene (N).

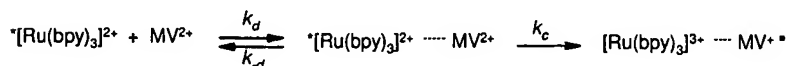
symmetrical  $[\text{PF}_6]^-$  anion. On the other hand, as suggested by the authors [14b] this enhanced ionic cross-linking probably results in a greater diffusing mass, and therefore a greater  $A$ , whilst creating large cavities for solutes to jump into.

A large and positive entropy of activation, confirming that the solvent ions are freed up on formation of an encounter complex, was also found by the same authors for the diffusive electron-transfer quenching of the excited state of tris(4,4'-bipyridyl)ruthenium,  $[\text{Ru}(\text{bpy})_3]^{2+}$ , by methylviologen,  $\text{MV}^{2+}$  (Scheme 5.1-2) [15].

The ionic liquid structure, determining viscosity, cohesive pressure and degree of order, therefore, seems to be the main factor affecting the rate of diffusion-controlled reactions, influencing both the enthalpy and the entropy of the process.

Electron and hydrogen transfer processes in ionic liquids have also been widely investigated in the last three to four years through pulse radiolysis [16]. Ionic liquids are excellent media for the generation of radical ions; electrons and holes may be generated in high yield by radiolysis of pure ionic liquids and electrons may be efficiently trapped by both cations and anions. Moreover, the tendency of ionic liquids to supercool, resulting in the formation of more viscous liquids and finally transparent glasses without crystallization, has been used for the generation and spectroscopic characterization of unstable solute radical ions [17], and then, after thermal annealing of the solvent up to ambient temperature, to study the reactivity of these transient species.

Kinetic studies of several electron transfer processes triggered via pulse radiolysis have provided additional information about the properties of these new reaction media. Using this method to generate radicals the rate constants measured in ionic liquids for many diffusion-controlled electron transfer reactions were lower than those measured in water or common organic solvents. Even in this case, however, the authors only partly attributed [16a] the low kinetic constants, found for example for the oxidation of chlorpromazine and Trolox by  $\text{CCl}_3\text{O}_2^*$ , to the high viscosity of the ionic liquids used,  $[\text{BMIM}][\text{PF}_6]$  and  $[\text{BMIM}][\text{BF}_4]$ . Considering that these reactions require separation and reassembly of solvent molecules, the effect has been primarily attributed to the high degree of ion-association of the ionic liquids investigated, and it has been suggested that, for these reactions, the rate constants



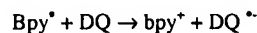
**Scheme 5.1-2** Diffusive electron-transfer quenching of the excited state of tris(4,4'-bipyridyl)ruthenium,  $[\text{Ru}(\text{bpy})_3]^{2+}$ , by methylviologen,  $\text{MV}^{2+}$ .

should be better correlated with the solvent cohesive pressure than with solvent polarity. "Ionic liquids are highly ordered reaction media, and the activation energies for the reactions carried out in ionic liquids can be high because it is necessary to break the order of the medium to bring all the components to the reaction site" [16a].

The kinetic studies of pulse radiolysis triggered electron transfer processes in pyridinium- and ammonium-based ionic liquids have confirmed the data arising from laser flash photolysis studies: i.e. that the rate of diffusion-controlled constants measured in ionic liquids are often higher than the rate constants estimated from the viscosity of the IL employed ( $k_{\text{diff}} = 8000RT/3\eta$ ). In this case, two different explanations have been given by the same authors for this experimental result. Initially, since kinetic constants higher than the estimated limits have been found for electron transfer reactions from the *N*-butylpyridinyl radical (BuPy<sup>•</sup>) to other substrates (methyl viologen, 4-nitrobenzoic acid and duroquinone, DQ), using an *N*-butylpyridium IL as solvent, the phenomenon was attributed to an electron hopping through solvent cations ([BuPy]). However, this behavior was also found for reactions that could not involve such a mechanism, i.e. the previously mentioned quenching of benzophenone triplet by naphthalene [14b], the reaction of solvated electrons with aromatic compounds, and the reaction of pyridinyl radicals (bpy<sup>•</sup>) with duroquinone (DQ) in ionic liquids having a completely different nature, such as ammonium salts {[Bu<sub>3</sub>MeN][Tf<sub>2</sub>N]} (Scheme 5.1-3) [18]. It has therefore been proposed [18] that the viscosity of ionic liquids, which determines the diffusion of whole molecules or ions, does not adequately represent the diffusion of reactants within ionic liquids.

In particular, it has been suggested that the highly ordered structure of these salts may contain voids, and that these voids can accommodate small solute molecules. Furthermore, since the chains present on the cations are flexible they can move more rapidly than the whole cation, permitting a rapid diffusion of solutes from one void to another [18]. The formation of cavities (voids) in ionic liquids has been recently studied via Monte Carlo simulations [19]. Analysis of cavity size distribution functions shows that ionic liquids exhibit a large tendency to form cavities; a property which seems to be correlated to the attractive interactions between ions and, particularly, to the tendency of the ions to associate into ion aggregates.

The presence of voids and the ability of small molecules to move within them have also been recently proposed to explain the reactivity of H<sup>•</sup> atoms with aromatic solutes in ionic liquids. Indeed, it has been shown [20] that the rate constants for reactions of pyrene and phenanthrene with H<sup>•</sup> atom are 10 times higher than for the reactions of the corresponding solvated electrons, implying that the diffusion-limited rate constant for the H<sup>•</sup> atom reaction is higher by one order of magnitude. Furthermore, for both substrates the trend in the ionic liquid examined, [Bu<sub>3</sub>MeN][Tf<sub>2</sub>N], is opposite to that observed in water, suggesting that a small



Scheme 5.1-3 Reaction of pyridinyl radicals (bpy<sup>•</sup>) with duroquinone (DQ).

1 neutral species, such as the  $H^\bullet$  atom, can move easily between voids within the ionic  
2 liquid, whereas the diffusion of solvated electrons, being charged species, is limited  
3 by their interaction with the ionic charges of the medium.

4 In conclusion, in agreement with other experimental measurements, the kinetic  
5 and thermodynamic data arising from the energy transfer, electron transfer and  
6 proton abstraction reactions suggest highly ordered structures for ionic liquids,  
7 well above their melting points. The highly ordered structure can affect reactivity  
8 through entropic effects, although the hypothesis of the presence of voids through  
9 which small molecules can move with the help of cation chains is very attractive.  
10 Based on this latter hypothesis, ionic liquids could be considered as reaction media  
11 characterized by a behavior that lies between that of true solvents and polymeric  
12 matrixes [21].

13 The extensive investigations [16] of Neta et al. have, however, also shown that other  
14 factors are able to affect the rate of electron transfer processes, particularly when  
15 charged species are involved and the solvent can influence reactivity by changing  
16 the energy of solvation of these species. The stability of  $Br_2^{\bullet-}$  is indeed much higher  
17 in  $[Bu_3MeN][Tf_2N]$  than in water and, consequently, the rate constant for oxidation  
18 of chlorpromazine by  $Br_2^{\bullet-}$  decreases upon changing the solvent from water to an  
19 IL [16e].  $[Bu_3MeN][Tf_2N]$  behaves like an aprotic organic solvent, with the energy of  
20 solvation of small ions being lower than in water and alcohols.

21 The concept of ionic liquids as ordered solvents, able to interact with charged  
22 species, has also been considered and developed by Hapiot et al. Initially  
23 these authors investigated [22] the stability of electrogenerated radical cations in  
24 imidazolium- and ammonium-based ionic liquids by cyclic voltammetry and used  
25 the current responses to extract the corresponding thermodynamic and kinetic pa-  
26 rameters, showing that the use of ionic liquids does not modify the mechanistic  
27 pathways of the reactions examined. The electron transfer rates for reactions be-  
28 tween aromatic molecules and the electrode decrease by an order of magnitude on  
29 going from molecular solvents to ionic liquids, an effect that has been attributed  
30 to a higher solvent reorganization during the charge transfer. On the other hand,  
31 the kinetics of the chemical reactions triggered by the electron transfer are only  
32 slightly affected by the use of ionic liquids. The only notable effect is a decrease in  
33 the bimolecular reaction rates, which has been attributed partly to a lowering of the  
34 diffusion-controlled kinetic rate constants together with a poorly specified "specific  
35 solvation effect" of reactants in these special media characterized by a high-degree  
36 of ion association.

37 More recently, the same authors studying the effects of the ionic liquids  
38 ( $[BMIM][Tf_2N]$ ,  $[Me_3BuN][Tf_2N]$  and  $[Et_3BuN][Tf_2N]$ ) on the cleavage reactivity  
39 of aromatic radical anions have given [23] more detailed information about the  
40 ability of ionic liquids to affect reactivity through "specific solvation effects"  
41 (Scheme 5.1-4). The reactivity of radical anions is considerably modified when  
42 changing from acetonitrile to an ionic liquid.

43 However, the effects mainly depend on the charge delocalization in the radical  
44 anion and the nature of the ionic liquid's cation plays a secondary role. When  
45 the charge is spread out over the entire molecule, as in the 9-chloroanthracene



Scheme 5.1-4 Cleavage reactivity of aromatic radical anions.

radical anion, the carbon–halogen bond cleavage accelerates in ionic liquids due to specific interaction (ion pairing) between the cation of the ionic liquid and the small leaving ion. On the contrary, in radical anions where the negative charge is more concentrated on a small area of the molecule, such as in the case of 4-chlorobenzophenone where it is mostly on the oxygen atom of the carbonyl group, a large decrease in the cleavage activity occurs on changing from acetonitrile to ionic liquids. This behavior has been attributed to the fact that, in this latter case, the stabilization of the leaving group still exists but it is largely overcompensated by the stabilization of the radical anion, in agreement with the positive shift of the reduction potential. Ion pair association stabilizes the  $\pi^*$  orbital where the unpaired electron is located and thus decreases its ability to be transferred into the  $\sigma^*$  of the breaking bond. This change in reactivity can be accompanied by a total change of mechanism and the dimerization between two charged radical anions can become favored over the cleavage reaction. It is noteworthy that a strong ion pairing between the imidazolium cation and the dinitrobenzene dianion was previously shown by cyclic voltametric measurements [24].

The question of “ion pairing” in ionic liquids is more complicated and quite different from that encountered in conventional solvents where ion pair association is built between a discrete ion surrounded by solvent molecules and another solvated species. In ionic liquids, there is no molecular solvent to solvate the ionic species. The solvent shell is ionic and an ionic species, dissolved or generated in an ionic liquid, should always be surrounded by the counteranions of the ionic liquid. The formation of clusters between cation(s) and anionic solutes (or between anion(s) and cation solutes) is a process that competes with the “intra-association” between the ions of ionic liquids and depends on their relative strengths.

#### 5.1.2.2 Diels–Alder Reactions

Important information about ionic liquid properties has also been obtained by the study of reactions occurring through isopolar transition states, such as Diels–Alder reactions. Diels–Alder reactions have been widely investigated in molecular solvents and it has been suggested that the hydrogen-bond donating capacity and the cohesive energy density of the solvent are the determining solvent properties able to affect both the kinetic and stereochemical behavior of these reactions. Diels–Alder reactions can indeed be efficiently performed using water as reaction medium [25]; in this solvent the rates and the endo/exo ratios (when they can be observed) are much higher than in common organic solvents.

Recently, ionic liquids have also been used with success as solvents for Diels–Alder reactions. The reactions in ionic liquids are indeed marginally faster

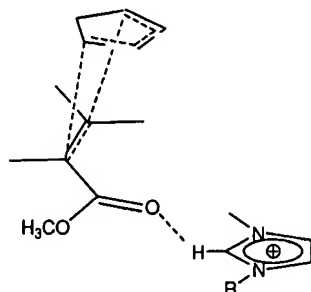
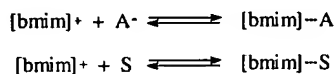


Fig. 5.1-1 Ability of the 1,3-dialkylimidazolium cation to hydrogen bond methyl acrylate in the course of its reaction with cyclopentadiene.

than in water but are considerably faster than in diethyl ether. Furthermore, it has been shown that, as with molecular solvents, the presence of a Lewis acid greatly accelerates the reaction and improves selectivity. The acidity of chloroaluminates [26], or ionic liquids containing  $\text{ZnCl}_2$  and  $\text{SnCl}_2$  [27], have been used to this purpose. The molecular origin of how ionic liquids influence this reaction is, however, always a matter of controversy. A solvophobic effect, able to generate an "internal pressure" and to promote the association in a cavity of the solvent, has been initially invoked to explain the kinetic and stereochemical behavior of Diels–Alder reactions carried out in ionic liquids [28,29]. A more recent study on the reaction of cyclopentadiene with methyl acrylate in several ionic liquids has, however, provided evidence that the ionic liquid's hydrogen-bond donor ability increases reactivity and selectivity [30]. Moreover, the determination of the selectivity in five  $[\text{BMIM}]^+$ -ionic liquids has shown that the nature of the anion also affects the endo/exo ratio. Higher selectivities characterize ionic liquids having the smaller hydrogen-bonding interaction between cation and anion. The *endo* selectivity has therefore been explained considering that the ability of the cation to hydrogen bond methyl acrylate is determined by two competing equilibria (Fig. 5.1-1).

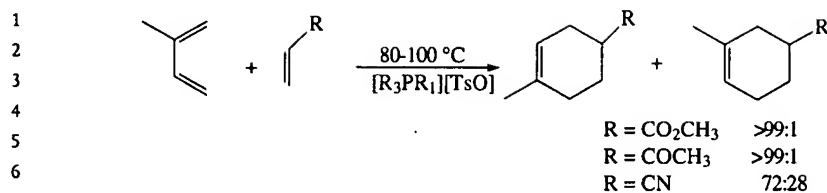
Since both anion (A) and solute (S) can be hydrogen bonded to the cation, the concentration of the bonded methyl acrylate is inversely proportional to the equilibrium constant for the formation of the cation–anion hydrogen-bonded adduct (Scheme 5.1-5).

These data, although they give important information about the hydrogen donor ability of 1,3-dialkylimidazolium ionic liquids, do not exclude the possibility that other factors can influence the rate and selectivity of Diels–Alder reactions. Recently, the kinetic study of reaction between the first excited state of molecular oxygen and



Scheme 5.1-5 Equilibria for the formation of the cation–anion hydrogen-bonded adduct vs. the cation–solute hydrogen-bonded adduct.

## 274 | 5 Organic Synthesis



8 **Scheme 5.1-6** Diels–Alder reactions of isoprene with methyl acrylate,  
9 acrylic acids, but-3-en-2-one and acrylonitrile in phosphonium tosylates.

10  
11 1,4-dimethylnaphthalene has shown [4] that the variation in reaction kinetic constants  
12 in the [BMIM]<sup>+</sup>-based ionic liquids examined arises from lower activation enthalpies  
13 associated with decreased cavitation volumes for the transition states with respect to  
14 solvated reagents. The kinetic constants increase with increasing solvent cohesive  
15 pressure. Although this reaction does not allow the investigation of the problem  
16 of the endo/exo ratio, the authors suggest that in the cases where there are two  
17 competing product-forming transition states, that with the most negative  $\Delta V_{\text{solv}}^\ddagger$   
18 should be increasingly favored as the cohesive pressure is increased, if this latter  
19 parameter is the dominant controlling factor. In other words, cohesive pressure  
20 might also significantly affect the reaction diastereoselectivity. Unfortunately, at the  
21 moment only few data of cohesive pressure for ionic liquids have been reported  
22 and, therefore, it is not possible to verify the role of this parameter on the selectivity  
23 of the previously reported Diels–Alder reactions.

24 It is finally worth noting that phosphonium tosylates [31], and more recently  
25 pyridinium-based ionic liquids [32], have also been used as solvents for the  
26 Diels–Alder reactions of isoprene with methyl acrylate, acrylic acids, but-3-en-2-  
27 one and acrylonitrile (Scheme 5.1-6).

28 In phosphonium salts the reactions of isoprene with oxygen-containing  
29 dienophiles proceed with high regioselectivity (>99:1), whereas in pyridinium-  
30 based ionic liquids selectivity and reactivity depend on the ionic liquid anion  
31 ([BF<sub>4</sub>]<sup>−</sup> < [CF<sub>3</sub>COO]<sup>−</sup>), on dienophile nature and on the reaction time. The high  
32 regioselectivity characterizing many of these reactions has been attributed in both  
33 cases to the ability of the ionic liquid to coordinate substituents on the dienophile.  
34 Unfortunately, in this case the possible role of solvent cohesive pressure cannot be  
35 evaluated, since the  $\delta^2$  values for pyridinium- and phosphonium-based ionic liquids  
36 are, as yet, unknown.

37  
38 5.1.339 **Ionic Liquid Effects on Reactions Proceeding through Dipolar Transition States**

40  
41 Hughes and Ingold, primarily studying substitution and elimination reactions,  
42 have extensively investigated the effect of molecular solvents on reactions passing  
43 through dipolar-transition states [2]. On the basis of a simple qualitative solvation  
44 model, which exclusively considers electrostatic interactions between ions (or dipol-  
45 ar molecules) and solvent molecules in initial and transition states it is generally

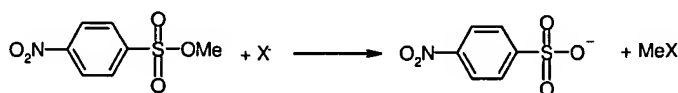


possible to predict the variations in reaction rates on changing the solvent. Despite the extensive and successful application of this theory, it does contain some inherent limitations. One of these limitations is the assumption that the reactions are controlled by enthalpy changes; the contribution of entropy changes to changes in Gibbs energy of activation are considered negligible. A second limitation concerns the fact that the solvent is treated as a dielectric continuum, able to interact with the solute molecules exclusively through non-specific interactions. Third, the model considers exclusively the static equilibrium transition-state solvation. Fourth, it neglects the changing solvent structure and therefore it ignores the related entropic contributions. In conventional media, interactions inside the solvents are generally small compared to solute-solvent interactions, but surely consideration should be given to solvent association when reactions are carried out in highly structured solvents, such as ionic liquids. It is possible that all of the limitations may be important in the case of ionic liquids, as we will see below.

#### 5.1.3.1 Nucleophilic Substitution Reactions

Nucleophilic substitution reactions in ionic liquids have recently been the subject of both synthetic [33] and kinetics and mechanistic studies [34]. Ionic liquids may be efficient promoting media for nucleophilic displacement reactions and important information about the ionic liquid properties has been obtained from the study of these reactions. The kinetic investigation of bimolecular substitution reactions of the halides on methyl *p*-nitrobenzenesulfonate, recently carried out [34] by Welton et al. in several ionic media characterized by the same anion,  $[\text{Tf}_2\text{N}]^-$ , and different cations ( $[\text{BMIM}]^+$ ,  $[\text{BMMIM}]^+$  and  $[\text{BMPY}]^+$ ) or by the same cation,  $[\text{BMIM}]^+$  and different anions ( $[\text{BF}_4]^-$ ,  $[\text{PF}_6]^-$ ,  $[\text{SbF}_6]^-$  and  $[\text{Tf}_2\text{N}]^-$ ), has shown that the halides' nucleophilicities depend on the ionic liquid structure (Scheme 5.1-7).

In molecular solvents, this reaction can proceed either through discrete anions or through ion pairs. The nucleophilic reactivity of an anion depends significantly on the degree of association with the cation and on the hydrogen-bond donor ability of the solvent. In ionic liquids, halides are coordinated by cations and the presence of "free" anions can be excluded, although coordinated anions are quite different from ion pairs in molecular solvents. In all of the ionic liquids examined the reactivity of chloride, bromide and iodide is lower than in chlorinated solvents, in agreement with the more polar nature of ionic liquids (as suggested by the Kamlet-Taft  $\pi^*$  parameter). Polar solvents should indeed disfavor reactions occurring through more charge diffuse transition states than reagents. The order of halide nucleophilicity is, however, affected by the ionic liquid cation and anion. In  $[\text{BMPY}][\text{Tf}_2\text{N}]$ ,



**Scheme 5.1-7** Bimolecular substitution reaction of methyl *p*-nitrobenzenesulfonate with halides.

the nucleophilicity scale is  $\text{Cl}^- > \text{Br}^- > \text{I}^-$ , in agreement with the known gas-phase nucleophilicity trend. In  $[\text{BMIM}][\text{Tf}_2\text{N}]$ , the scale is  $\text{I}^- > \text{Br}^- > \text{Cl}^-$ , indicating that some influence of the IL is acting differentially on the three halides, whereas in  $[\text{BMMIM}][\text{Tf}_2\text{N}]$  the situation is in some way intermediate, with nucleophilicity changing  $\text{Cl}^- > \text{I}^- > \text{Br}^-$ . The differences in the kinetic constants on going from one ionic liquid to the next are, however, very small, except where the halide is chloride. Since chloride is the best hydrogen-bond acceptor of the halides, it is highly probable that its nucleophilicity is mainly affected by the ability of the cation to interact through hydrogen bonding with chloride. The halides nucleophilicity is also affected by the anion nature: in  $[\text{BMIM}][\text{PF}_6]$  chloride is more nucleophilic than bromide. In  $[\text{BF}_4]^-$  and  $[\text{SbF}_6]^-$  ionic liquids, chloride and bromide have practically the same nucleophilicity, whereas in ionic liquids having  $[\text{OTf}]^-$  and  $[\text{Tf}_2\text{N}]^-$  as anions, the chloride is less nucleophilic than the bromide. Iodide is generally more nucleophilic than bromide, although in  $[\text{BMIM}][\text{Tf}_2\text{N}]$  they have similar nucleophilicity. It is evident that when the ionic liquid anion is a good hydrogen-bond acceptor (higher  $\beta$  value), it may compete with the halide to form a hydrogen bond with the cation, and an effect on halide nucleophilicity can be expected. However, the correlation between the kinetic constants measured in the different ionic liquids and the  $\beta$  parameter is not complete, suggesting the influence of other solvent effects.

A strong cation–anion association in the ionic liquid can affect not only the ability of the cation to give hydrogen bonding but more generally, it can modify the degree of association of the cation to the nucleophile, affecting both the activation enthalpy and entropy of the process. Evidence in support of this latter hypothesis has been obtained [34] from the examination of the activation parameters. The activation parameters found for the reaction of chloride and bromide in different ionic liquids have been rationalized [34] by considering that, in these bimolecular reactions ( $\text{S}_\text{N}2$ ), the halide is coordinated to several cations and the enthalpies are generally very similar to those characterizing the reactions via ion pairs in dichloromethane. The activation entropies (often large and negative) are, however, more similar to those found in molecular solvents for free ions (large and negative) than ion pairs (positive). This different behavior between entropy and enthalpy has been explained [34] by considering that the reaction occurs through a pentacoordinate transition state. The activation step is an association process, which should have negative entropy. In dichloromethane, it has a positive value because, when the activated complex is formed, the cation of this ion pair is liberated as a free solvated cation and the leaving group cannot be stabilized by ion pairing (Fig. 5.1-2).

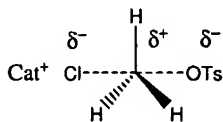
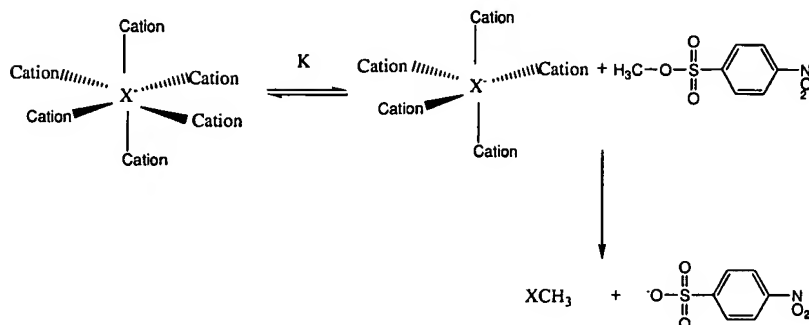


Fig. 5.1-2 Transition state in the bimolecular substitution reaction of methyl *p*-nitrobenzenesulfonate with chloride.

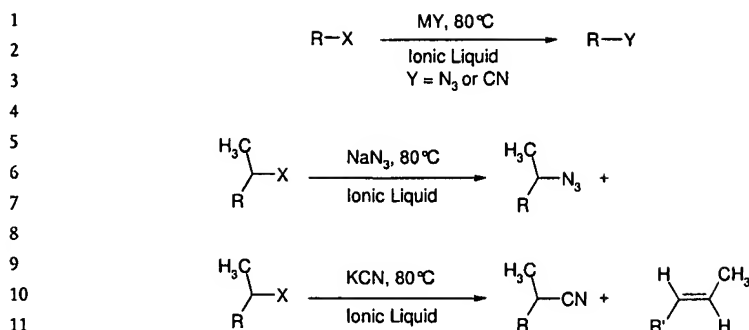


**Scheme 5.1-8** Equilibrium between fully coordinated "unavailable" chloride and a one face "available" chloride in the bimolecular substitution reaction of methyl *p*-nitrobenzenesulfonate with chloride.

In ionic liquids, the leaving group associates instead with the ionic liquid's cation(s). The entropy gained by liberating a cation is cancelled out by the association of another cation with the leaving group. It is, however, interesting to note that the enthalpy and entropy change significantly on changing the ionic liquid's anion. In particular the reactions in [BMIM][BF<sub>4</sub>] are accompanied by particularly large entropic barriers. This behavior has been interpreted [34c] considering that in the ionic liquid an equilibrium exists between fully coordinated "unavailable" chloride and a one face "available" chloride which can associate with the substrate (Scheme 5.1-8).

This loose association of available chloride with the substrate should represent the ground state. The dissociation of the cations from the halide to a greater or lesser degree compensates for the loss of entropy arising from the S<sub>N</sub>2 mechanism. If the anion-cation linkages are relatively strong (as in the case of [BMIM][BF<sub>4</sub>]), the halide is more weakly coordinated and its reaction will be characterized by a lower activation enthalpy associated with a larger activation entropy.

Although ionic liquids have also been used as solvents for alkane fluorination through nucleophilic substitution processes, no quantitative data about this reaction have been reported [35]. The preparative experiments carried out under non-identical conditions cannot be easily compared with each other. However, they seem to suggest that the nucleophilicity and basicity of the fluoride anion in ionic liquids depends on the counteranion and on the presence of cosolvents and water. In the presence of acetonitrile and small amounts of water, the reactions using RbF or CsF proceed much faster than the reaction of KF. In the absence of cosolvents and water, KF practically does not react with alkyl bromides whereas CsF gave mixtures of substitution and elimination products. Moreover, under these conditions a slow degradation of the ionic liquid due to the basicity of CsF has been observed. The different reactivity of the metal fluorides is probably determined by the tightness of the ion pairs, a parameter influenced also by the presence of water in the reaction media. It is, moreover, notable that KF in 1,3-dialkylimidazolium methanesulfonates, in the



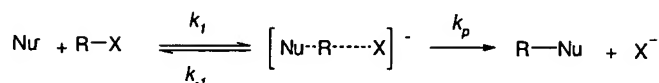
**Scheme 5.1-9** Reactions of alkyl halides or tosylates with KCN and NaN<sub>3</sub> in different ionic liquids.

absence of cosolvents or added water, has been used successfully as a catalyst for the esterification of carboxylic acids with alkyl halides (generally chlorides) [36]. Under these conditions KF is not able to act as a nucleophile but its interaction with the carboxylic acid through a strong hydrogen bond with the hydroxy proton increases the nucleophilicity of the organic part of the complex and favors the reaction of the acid with the alkyl halide. The ionic liquid behaves in this case as a polar aprotic solvent.

In this research field, the shift of the substitution mechanism from S<sub>N</sub>2 to S<sub>N</sub>1 and the competition between substitution and elimination have recently been investigated [37]. The reactions of primary, secondary and tertiary halides or tosylates with KCN and NaN<sub>3</sub> in [BMIM][PF<sub>6</sub>], [BMIM][Tf<sub>2</sub>N] and [HPY][Tf<sub>2</sub>N] were examined (Scheme 5.1-9). The observed ability of Cl<sup>−</sup>, Br<sup>−</sup>, I<sup>−</sup>, and tosylate to act as leaving groups in the substitution reaction of NaN<sub>3</sub> is similar to that reported for the same process in cyclohexane (it exactly corresponds to that calculated for S<sub>N</sub>2 reactions in the gas phase), suggesting the absence of strong specific interactions between the examined ionic liquids and the activated complex. The high reactivity of the examined secondary substrates (secondary ≥ primary) in the reaction of NaN<sub>3</sub> in ionic liquids disagrees with a pure S<sub>N</sub>2 mechanism, although the exclusive formation of substitution products with complete inversion of configuration excluded the S<sub>N</sub>1 mechanism for these substrates.

Considering, therefore, the overall reaction order and the product distribution, it has been suggested [37] that the reaction of NaN<sub>3</sub> in ionic liquids occurs with a gradual shift of the mechanism from S<sub>N</sub>2 to S<sub>N</sub>1, depending on the substrate. The reaction should proceed through the rear-side nucleophilic attack of N<sub>3</sub><sup>−</sup> with a pure S<sub>N</sub>2 mechanism in the case of primary substrates. A pure S<sub>N</sub>1 mechanism probably occurs in the case of tertiary substrates, whereas the reaction of secondary halides and tosylates implies “the nucleophilically assisted formation of an ion pair intermediate.” Practically, in the case of secondary substrates the bond-making and bond-breaking in the transition state are not two synchronous processes but the latter precedes the former (Scheme 5.1-10).

Evidence in favor of a larger amount of carbocation character in the transition state of secondary substrates in ionic liquids has also been obtained by comparison



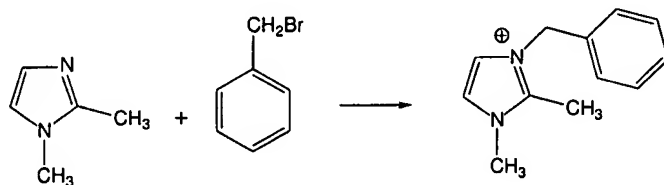
Scheme 5.1-10 Nucleophilically assisted formation of an ion pair intermediate.

of the reaction of 2-bromoheptane with  $\text{CN}^-$  and  $\text{N}_3^-$ . The reactivity order of 2-bromoheptane ( $\text{N}_3^- \gg \text{CN}^-$ ) is opposite to that observed [38] in molecular solvents for displacement reactions on methyl halides (pure  $\text{S}_{\text{N}}2$  reaction), but the same as for nucleophilic reactions with carbocations.

Recently, the classical Menshukin reaction between two neutral reagents has also been investigated in several ionic liquids [39, 40]. In the first study by Skrzypczac and Neta, the kinetic constants for the reaction of 1,2-dimethylimidazole with benzylbromide were determined [39] in twelve ionic liquids and a comparable number of molecular solvents (Scheme 5.1-11).

Whereas the rate constants in molecular solvents vary by two orders of magnitude on going from 1-propanol to acetonitrile, the variation in the ionic liquids examined was less than a factor of three and the values are similar to the highest two values in molecular solvents, i.e. in acetonitrile and propylene carbonate. The variations within the ionic liquids indicate a small effect of the anion ( $[\text{TF}_2\text{N}]^- < [\text{PF}_6]^- < [\text{BF}_4]^-$ ) and a moderate effect of cation (adding a methyl at C-2 of the imidazolium ring increases the rate constant slightly) and the observed trend is in agreement with a negative contribution of the ionic liquid's hydrogen-bond donor ability. Whereas the dipolarity/polarizability of ionic liquids stabilizes the transition state of this reaction, the ionic liquid's hydrogen-bond acidity decreases the nucleophilicity of 1,2-dimethylimidazole. The correlation of the rate constants with the solvatochromic parameter  $E_{\text{T}}(30)$  is, however, reasonable within each group of similar solvents but very poor when all the solvents are correlated together. Really, for the organic solvents a better correlation has been obtained using a combination of two parameters,  $\pi^*$  (dipolarity/polarizability) and  $\alpha$  (hydrogen-bond acidity) but this approach was not tried for ionic liquids, for which only the  $E_{\text{T}}(30)$  parameter was known at the time.

In the light of the more recently reported data about the alkylation of tertiary amines (see discussion reported below) [40], I have tried to correlate the rate



Scheme 5.1-11 Reaction of 1,2-dimethylimidazole with benzyl bromide.

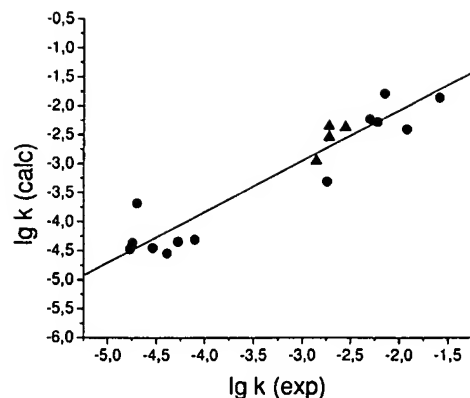


Fig. 5.1-3 Multiparameter correlation of the rate constant for the reaction of 1,2-dimethylimidazole with benzyl bromide with  $\pi^*$ ,  $\delta^2$  and  $\alpha$  solvent parameters. Molecular solvents ( $\bullet$ ), IL ( $\blacktriangle$ ).

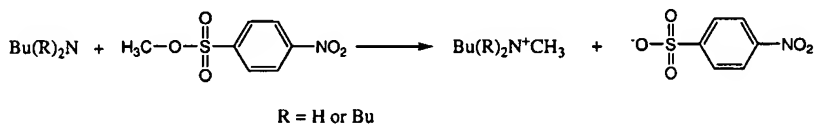
constants in ionic liquids with the parameters  $\pi^*$ ,  $\alpha$  and  $\delta^2$ . These parameters should take into account not only the dipolarity/polarizability and the hydrogen-bond donor ability but also the anion–cation association. Since all three parameters are known for only a limited number of ionic liquids, the correlation has been verified by also using the data related to the reactions in molecular solvents. The correlation (Fig. 5.1-3) fits Eq. (5.1-1)

$$\log k = -4.27 + 2.13\pi^* - 2.71\alpha + 1.37 \times 10^{-3}\delta^2 \quad (5.1-1)$$

with a correlation coefficient  $r^2 = 0.93$ .

The dependences on  $\pi^*$ ,  $\delta$  and  $\alpha$  have quite small uncertainties, respectively  $\pm 19\%$ ,  $\pm 44\%$ ,  $\pm 15\%$ , showing that all three parameters contribute to the overall reaction rate. Furthermore, the inclusion of the values related to the ionic liquids drastically decreases the uncertainty of the dependence on  $\delta^2$  (from  $\pm 800\%$  to  $\pm 44\%$ ) and this parameter, which can be neglected in the case of molecular solvents, becomes important to improve the correlation when ionic liquids are included.

The data arising from the kinetics of the reaction of three *n*-butylamines (mono, di, tri-substituted amines) with methyl *p*-nitrobenzene sulfonate in a variety of



Scheme 5.1-12 Reaction of butylamines with methyl *p*-nitrobenzene sulfonate in different ionic liquids.

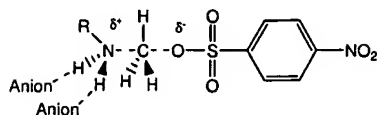


Fig. 5.1-4 Transition state of the reaction of alkylamines with methyl *p*-nitrobenzene sulfonate.

ionic liquids, acetonitrile and dichloromethane are also in agreement with this analysis (Scheme 5.1-12).

All amines are more nucleophilic in ionic liquids than in the molecular solvents. The Eyring activation parameters reveal that the changes in the activation entropies are mainly responsible, which can be at least partially rationalized on the basis of the differing hydrogen-bonding abilities of ionic liquids, as expressed by the Kamlet-Taft solvent parameters. Reactions of amines in ionic liquids are accelerated by the high polarizability/dipolarity term,  $\pi^*$ , characterizing these solvents (in agreement with the previously reported correlation). Moreover, where the formation of hydrogen bonds between a nucleophile and the anion of an ionic liquid is possible (primary and secondary amines), the reaction is further accelerated by the hydrogen-bonding ability of the ionic liquid (Fig. 5.1-4).

This is unlike the formation of hydrogen bonds between the nucleophile and the cation, possible for all amines, which tends to reduce the reactivity of the nucleophile and should be avoided (in accord with the sign of the  $\alpha$  parameter in Eq. (5.1-1)). On the other hand, the kinetic data and the thermodynamic parameters related to the reaction of  $\text{Bu}_3\text{N}$  in  $[\text{BMPY}][\text{OTf}]$  suggest also that, where there is no opportunity for the nucleophile to hydrogen bond to either the anion or cation of the ionic liquid, other effects such as the self-association of the ionic liquid may become important. Related to this feature, it has been suggested [40] that the inability of the reagents to disrupt the Coulombic attraction of the ionic liquid's ions may leave them with a restricted volume in which to move, producing a solvatophobic effect. Furthermore, since the activated complex is a species containing both  $\delta^+$  and  $\delta^-$  moieties, it is capable of interacting with the ionic liquid's ions. In so doing, it may disrupt the interionic interactions and cause the local structure of the ionic liquid to break down, producing an increase in activation enthalpy and entropy ( $\Delta S^\ddagger$  becomes less negative) (Fig. 5.1-5).

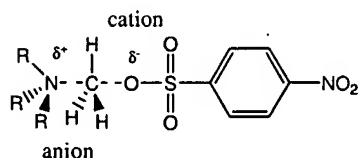
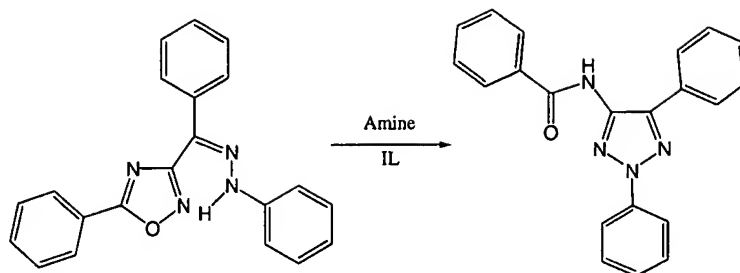


Fig. 5.1-5 Transition state of the reaction of alkylamines with methyl *p*-nitrobenzene sulfonate; possible interactions in an ionic liquid.



**Scheme 5.1-13** Rearrangement of the Z-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole in ionic liquids.

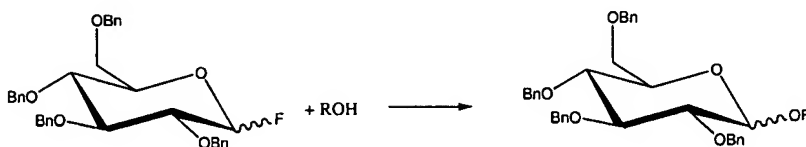
In agreement with the behavior of amines, the reactivity of other neutral nucleophiles, such as water and methanol, towards primary and secondary haloalkanes in ionic liquids is generally higher than in molecular solvents and lower amounts of elimination products are formed. Water and methanol are more nucleophilic but less basic in ionic liquids than in molecular solvents [41].

The inability of ionic liquids to interact strongly with neutral nucleophilic species has been considered recently to be the main factor determining the high rate of rearrangement of the Z-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole in ionic liquids in comparison to molecular solvents (Scheme 5.1-13) [42].

This intramolecular ring to ring rearrangement, induced by amines, has been investigated in [BMIM][PF<sub>6</sub>] and [BMIM][BF<sub>4</sub>]. With the exception of an acid-base equilibrium between the solvent and amine, the data seem to indicate that other interactions (such as substrate-ionic liquid, amine-ionic liquid and amine-amine) have scarce relevance, whereas the high dipolarity/polarizability of ionic liquids stabilizes the rate-determining transition state and so increases the reaction rate.

In comparison to bimolecular nucleophilic substitutions, the monomolecular reaction (S<sub>N</sub>1) in ionic liquids has been less extensively investigated. The recent work on the glycosidation of glucopyranosyl fluoride, in the presence of acids has, however, given important information about this kind of reaction (Scheme 5.1-14). The stereoselectivity of the glycosidation of glucopyranosyl fluoride is significantly affected by the ability of the ionic liquid anion to interact with the positively charged intermediate [43].

This reaction, which takes place through an S<sub>N</sub>1 type mechanism, involves an oxonium intermediate and, since no epimerization of the generated glycosidic bond



**Scheme 5.1-14** Glycosidation of glucopyranosyl fluoride.



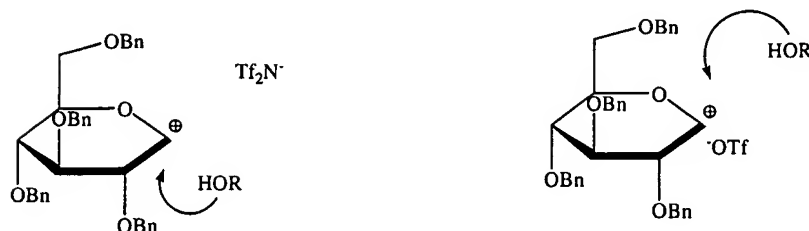


Fig. 5.1-6 Transition states of the  $S_N1$  type glycosidation of glucopyranosyl fluoride in presence of  $[\text{OTf}]^-$  and  $[\text{OTf}]^-$  anions, respectively.

occurs during the reaction, the product distribution may be considered to be under kinetic control. In  $[\text{HMIM}][\text{NTf}_2]$ , containing  $\text{HNTf}_2$ , the reaction is characterized by an  $\alpha$ -stereoselectivity, attributable to the anomeric effect; the alcohol attacks the oxonium ion preferentially on the  $\alpha$  face. However, using  $[\text{HMIM}][\text{ClO}_4]/\text{HCl}_4$  or  $[\text{HMIM}][\text{OTf}]/\text{HOTf}$  as solvent, the stereoselectivity inverts ( $\beta$ -stereoselectivity) and this behavior may be rationalized considering a stronger coordination of the perchlorate or trifluoromethanesulfonate with the oxonium intermediate (on the  $\alpha$ -face) which drives the alcohol attack on the  $\beta$ -face (Fig. 5.1-6).

It is noteworthy that experiments carried out using acids having a different anion with respect to the ionic liquid show that the  $\beta$ -stereoselectivity is induced exclusively by the anion of the ionic liquid, i.e. by its coordination with the positively charged intermediate. This behavior shows that, independently of the acid determining the formation of the oxonium intermediate, the metathesis reaction is so efficient that the anion of the ionic liquid is always the sole effective counteranion of the oxonium intermediate. The fact that the ionic intermediates undergo a very fast anion exchange is important, not only for the product distribution but also for the kinetic behavior of this kind of reaction. Although in ionic liquids the carbenium ion intermediates are always present as "ion pairs" or "ion aggregates" the rapid exchange of the anion renders the internal return of the primarily formed intermediates unimportant; the kinetic behavior of these species in ionic liquids should be more similar to those characterizing molecular solvents "solvent separated ion pairs" or "free" ions.

Finally, the data related to the application of ionic liquids for the cleavage of ethers are also notable. Chloraluminates [44], anhydrous hydrobromic acid in 1-methylimidazole [45] and concentrated hydrobromic acid in  $[\text{BMIM}][\text{BF}_4]$  or  $p$ -TsOH/ $[\text{BMIM}][\text{Br}]$  in  $[\text{BMIM}][\text{BF}_4]$  [46] have been used to regenerate phenols from the corresponding aryl alkyl ethers. In ionic liquids, in the presence of an efficient proton donor ( $\text{HBr}$  or  $\text{TsOH}$ ), the bromide anion behaves as a strong nucleophile able to cleave ethers. These latter reactions seem, therefore, to indicate that, as opposed to the situation in the absence of acids, the nucleophilicity of the bromide anion in ionic liquids in the presence of proton donors is higher than in molecular solvents (both protic and aprotic). This behavior may be a consequence of a

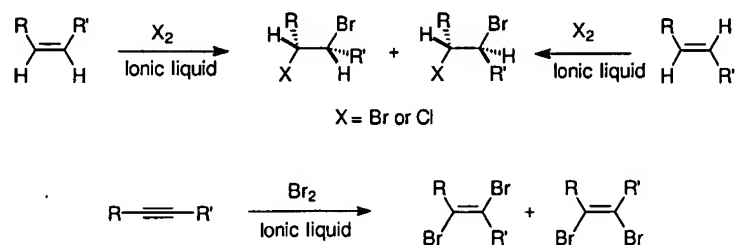
different acidity of HBr in ionic liquids with respect to molecular solvents, associated with the different solvation ability of the two reaction media. In water, HBr is highly dissociated but  $\text{Br}^-$  is strongly solvated; conversely, in chlorinated solvents  $\text{Br}^-$  is much less solvated and therefore more nucleophilic, but HBr is practically undissociated. Ionic liquids might represent a good compromise between these two opposite situations.

The increased nucleophilicity of halides ( $[\text{BMIM}]\text{X}$ ) in the presence of Brønsted acids has also been used to convert alcohols into alkyl halides under mild conditions. Since the mechanism of this reaction should involve the initial protonation of the OH group followed by nucleophilic displacement, the observed increase in the reaction rate may be attributed to an increased acidity of HBr associated with a higher nucleophilicity of  $\text{Br}^-$ , together with an enhanced ability of the ionic liquid to aid the charge separation in the transition state [47].

### 5.1.3.2 Electrophilic Addition Reactions

Electrophilic addition reactions are another class of reactions that have been extensively studied in organic solvents from a mechanistic point of view and bromine addition is one of the most investigated addition reactions. Chiappe et al. have used ionic liquids to synthesize vicinal dihaloalkanes and dihaloalkenes by electrophilic addition of halogens to double and triple bonds (Scheme 5.1-15) [48–50]. Recently, dibromides have also been synthesized [51] in ionic liquids using electrogenerated bromine, whereas bromohydrins have been obtained [52] under two-phase conditions (water/IL) through a vanadium (V) catalyzed oxidation of bromide ions by hydrogen peroxide.

Bromine addition in  $[\text{BMIM}][\text{PF}_6]$  and  $[\text{BMIM}][\text{BF}_4]$  is a stereospecific *anti*-addition process with dialkyl substituted alkenes, alkyl substituted alkynes and *trans*-stilbenes, whereas *cis*-stilbenes and aryl alkynes give mixtures of *syn*- and *anti*-addition products, although in the case of *cis*-diaryl substituted olefins the *anti*-stereoselectivity is generally higher than in chlorinated solvents. In the case of diaryl substituted olefins, such as stilbenes, it has been shown that stereoselectivity in molecular solvents depends primarily on two factors: (i) the nature of the intermediates; and (ii) the lifetime of the ionic intermediates [53]. Bridged bromiranium



**Scheme 5.1-15** Synthesis of vicinal dihaloalkanes and dihaloalkenes by electrophilic addition of halogens to double and triple bonds in various ionic liquids.

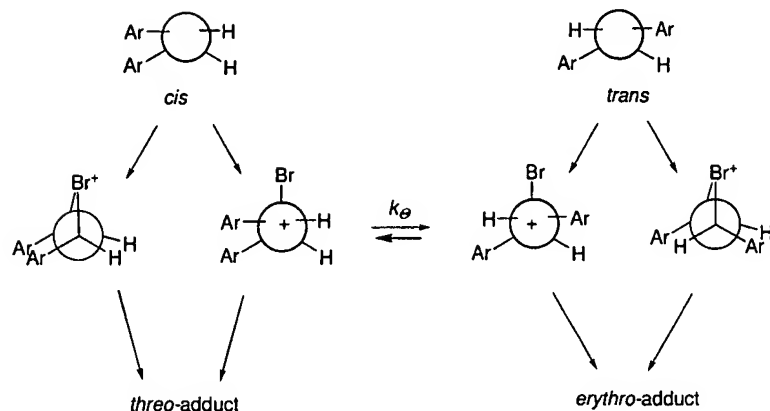
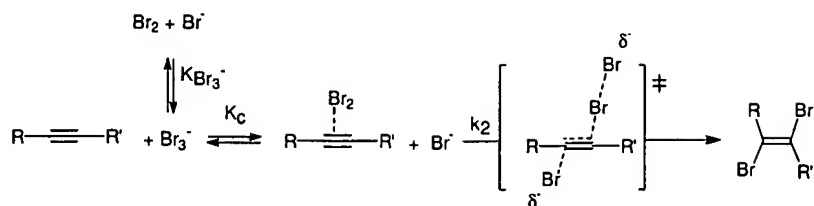


Fig. 5.1-7 Transition states in the electrophilic addition of bromine to stilbenes.

ions give exclusively *anti*-addition products, whereas open  $\beta$ -bromocarbenium ions generally give mixtures of *syn*- and *anti*-addition products. The nature of the intermediate is determined by the nature of the substituents on the phenyl ring, electron-withdrawing groups favor bridged intermediates, electron-donating groups open  $\beta$ -bromocarbenium ions. Open  $\beta$ -bromocarbenium ions give the *syn*-addition products mainly through an attack *anti* to the counter anion, after rotation around the C-C bond ( $k_\theta$ ) (Fig. 5.1-7). If the lifetime of the intermediate is sufficiently short, the rotation around the C-C bond is not able to compete with the nucleophilic attack of the counter anion and the *anti*-addition product can be obtained practically exclusively.

In molecular solvents, the nature of the ionic intermediate is not dependent on the properties of the solvent, whereas the lifetimes of the ionic intermediates are. In ionic liquids the nature of the intermediate is probably also not affected by the medium, whereas it does affect the lifetime of the intermediate or the rotation around the C-C bond, favoring the nucleophilic trapping of the first formed bromocarbenium ion.

The electrophilic additions of trihalide species ( $\text{Br}_3^-$ ,  $\text{ICl}_2^-$  and  $\text{IBr}_2^-$ ) to double and triple bonds have also been investigated. Ionic liquids having a trihalide as their anion have been prepared recently [50] by mixing equimolar amounts of halogens ( $\text{ICl}$ , or  $\text{IBr}$ , or  $\text{Cl}_2$  or  $\text{Br}_2$ ) to proper 1-alkyl-3-methylimidazolium halides, and the structures of the trihalide ions formed have been investigated by electrospray ionization mass spectroscopy (ESI-MS), UV and NMR. Spectroscopic measurements and reactivity data have shown that liquids bearing  $[\text{Br}_3]^-$ ,  $[\text{I}_3]^-$ ,  $[\text{IBr}_2]^-$  and  $[\text{ICl}_2]^-$  as counteranion are quite stable, whereas those having  $[\text{Br}_2\text{Cl}]^-$ ,  $[\text{I}_2\text{Cl}]^-$  and  $[\text{I}_2\text{Br}]^-$  as anions are rather unstable, since these latter anions tend to disproportionate into the more stable trihalide species. Unlike protic molecular solvents, which favor dissociation due to the very high energy of solvation of the small  $\text{Br}^-$  or  $\text{Cl}^-$  anions, ionic liquids seem to disfavor this process. Their behavior is, therefore, significantly different from alcohols or water.

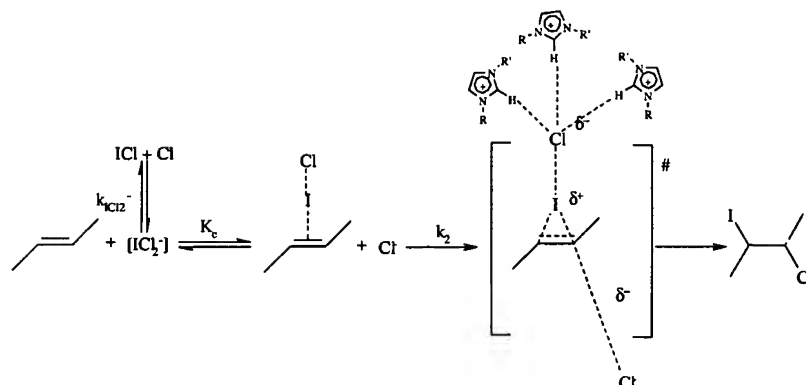


**Scheme 5.1-16** Electrophilic addition of  $\text{Br}_3^-$  to alkynes.

Electrophilic additions of  $\text{Br}_3^-$  to alkenes and alkynes have been carried out [48–50] both in  $[\text{BMIM}][\text{Br}]$  and in other ionic liquids bearing non-nucleophilic anions (Scheme 5.1-16). The reaction is always completely *anti*-stereospecific, independent of alkene or alkyne structure. It follows a second-order rate law, suggesting a concerted mechanism of the type reported for  $\text{Br}_3^-$  addition in aprotic molecular solvents, involving a product- and rate-determining nucleophilic attack by bromide on the alkene or alkyne- $\text{Br}_2$   $\pi$ -complex initially formed.

Since, in chlorinated solvents,  $\text{Br}_3^-$  addition is positively affected by the ability of the medium to hydrogen bond, the kinetic constants for the addition of  $\text{Br}_3^-$  to alkynes and alkenes have been measured in several ionic liquids having different hydrogen-bond abilities [49, 54]. Unlike the behavior observed in chlorinated solvents, however, no correlation has been found between the kinetic constants or the activation parameters and the ionic liquid's solvent parameters ( $\pi^*$  or  $\alpha$ ). The reaction in ionic liquids has, however, some important features with respect to those in molecular solvents. In particular, whereas in chlorinated solvents bond making is not influenced by the solvent hydrogen-bond ability, since the entering bromide ion is present as an ion pair with the tetraalkylammonium cation, in ionic liquids both bond breaking and bond making are affected by this property. Considering, moreover, that in this reaction both events (bond breaking and bond making) probably occur simultaneously in the rate-determining transition state only a very little effect, if any, may be detected.

The kinetic behavior for the addition of  $\text{ICl}_2^-$  to alkenes and alkynes is quite different. The mixed trihalide ionic liquids, in particular  $[\text{RMIM}][\text{ICl}_2]$  and  $[\text{RMIM}][\text{IBr}_2]$ , have been used as excellent iodine-donor reagents for the stereoselective *anti*-iodination of alkenes and alkynes in  $[\text{BMIM}][\text{PF}_6]$  [50]. Very good to almost quantitative yields of vicinal iodochloro or iodobromo adducts were observed for all of the substrates examined. However, kinetic measurements carried out in several ionic media, using  $[\text{BMIM}][\text{ICl}_2]$  as the reactant, have shown [54] that the addition of  $\text{ICl}_2^-$  is affected much more by the physicochemical properties of the ionic liquid under investigation than the addition of  $\text{Br}_3^-$ , and in this case a possible role of the hydrogen-bonding donor ability of the ionic liquid has been suggested. The reaction is indeed characterized by a relatively low activation enthalpy, associated with a high activation entropy, when the addition process is performed in  $[\text{BMIM}][\text{Tf}_2\text{N}]$  (the ionic liquid among those examined with a relatively higher hydrogen-bonding donor ability). Conversely, when the reaction is performed in liquids characterized



**Scheme 5.1-17** Addition of  $\text{ICl}_2^-$  to alkenes in a 1,3-dialkylimidazolium ionic liquid.

by cations less able to be hydrogen-bond donors, such as  $[\text{BMMIM}][\text{Tf}_2\text{N}]$  and  $[\text{BPY}][\text{Tf}_2\text{N}]$ , the activation enthalpies increase significantly and activation entropies decrease. It is also interesting to note that a high activation enthalpy, associated with a low activation entropy, has been found in  $[\text{BMIM}][\text{PF}_6]$ . This behavior may be rationalized considering the high degree of order characterizing this ionic liquid, which may affect the kinetics of this reaction mainly through entropic effects.

Finally, the different sensitivity of addition processes of the two trihalides ( $\text{Br}_3^-$  and  $\text{ICl}_2^-$ ) to the ionic liquid properties is probably a consequence of the different charge development into the two transition states. The addition of  $\text{ICl}_2^-$  is most likely characterized by a later transition state, having a greater iodonium character, and the attack by chloride is not itself the rate-determining step (Scheme 5.1-17). The ability of the ionic liquid to be a hydrogen-bond donor can indeed affect the reaction rate only in the case where bond breaking precedes bond making.

### 5.1.3.3 Electrophilic Substitution Reactions

Electrophilic aromatic substitutions are reactions of great importance for industry and ionic liquids have been used in these reactions as alternative reaction media, mainly with the aim of reducing the environmental impact of these processes. Only few reactivity data, which might be used to quantitatively estimate the effect of the ionic reaction medium on these reactions, have been collected.

Electrophilic nitrations of aromatics have been performed in several ionic liquids but, as shown [55] by Laali, depending on the nitrating agent and the ionic liquid, nitration of the solvent may compete with the electrophilic substitution of the substrate. This problem has been recently underlined [56] by Lancaster: high yields of aromatic nitration products using  $\text{HNO}_3\text{--Ac}_2\text{O}$  have been obtained mainly in  $[\text{BMPY}][\text{TF}_2\text{N}]$ , which has no aromatic cation. Using this nitrating agent, moreover, reaction of deactivated substrates is highly favored in ionic liquids with respect to molecular solvents. On going from dichloromethane to  $[\text{BMPY}][\text{TF}_2\text{N}]$  the yield of

1 bromonitrobenzene increases from 0 to 63%. Although no kinetic study has been  
2 performed on this reaction, the authors suggested that the increased reactivity might  
3 be attributed generically to the increased polarizability/dipolarity of the medium,  
4 although they do not exclude the contribution of specific interactions. [BMPY][TF<sub>2</sub>N]  
5 might favor the dissociation of acetyl nitrate to nitronium acetate (the nitronium  
6 ion is the nitrating agent) or it could interact more strongly with the Wheland  
7 intermediate. A more recent comparison [57] of the behavior of the reaction in  
8 [BMPY][TF<sub>2</sub>N] with that in [BMPY][OTf] has also shown that the anion affects the  
9 reaction; [BMPY][TF<sub>2</sub>N] is a better solvent for aromatic nitration. This effect has  
10 been attributed to the ease of formation of the nitronium ion in the former solvent,  
11 a feature which is consistent with the fact that [BMPY][TF<sub>2</sub>N] is a weaker hydrogen-  
12 bond acceptor than [BMPY][OTf].

13 Halogenated aromatic compounds are key intermediates in organic synthesis  
14 as they are precursors to a number of organometallic species used for the prepara-  
15 tion of highly functionalized molecules. Several electrophilic halogenation reactions  
16 have been performed in ionic liquids, although again no systematic mechanistic  
17 study has been reported. Regioselective brominations in ionic liquids have been  
18 carried out both using NBS [58] or tribromide-based ionic liquids (pentylpyrid-  
19 ium perbromide [59], [BMIM][Br<sub>3</sub>] and [HMIM][Br<sub>3</sub>] [60]). Although products are  
20 generally obtained in high yields in the case of tribromide-based liquids a higher  
21 efficiency of 3-methylimidazolium tribromide ([HMIM][Br<sub>3</sub>]), with respect to the  
22 corresponding non-acidic derivative [BMIM][Br<sub>3</sub>], has been observed [60]. Using  
23 [HMIM][Br<sub>3</sub>], the halogenation is effective not only with activated compounds, but  
24 also with differently substituted benzaldehydes as well as with sterically hindered  
25 aromatic compounds. Moreover, it is notable that no phenol is detected from the  
26 halogenation of anisole catalysed by [HMIM][Br<sub>3</sub>], although 3-methylimidazolium  
27 bromohydrogenate ([HMIM][HBr<sub>2</sub>]), the residue ionic liquid at the end of the reac-  
28 tion, has been used [45] in a 1:2 molar ratio to cleave the ether functionality.

29 Fluorinated arenes have instead been prepared using N-F fluorine transfer  
30 reagents, such as F-TEDA-BF<sub>4</sub> [61]. Substrate selectivity measured in com-  
31 petitive experiments carried out for the electrophilic fluorination of arenes  
32 ( $k_{\text{mesitylene}}:k_{\text{durene}}$ ), using F-TEDA-BF<sub>4</sub> (Selectfluor<sup>TM</sup>) as the halogenating agent,  
33 has suggested [62] that the reaction occurs through a polar mechanism, involving an  
34 ionic intermediate ( $\sigma$ -complex) and an ionic transition state in the rate-determining  
35 step. Comparison with the reaction in acetonitrile has, furthermore, suggested a  
36 slightly greater degree of polar character in the ionic liquid.

37 The same reagent, F-TEDA, in the presence of iodine in imidazolium and pyri-  
38 dinium ionic liquids has also been used [63] for the regioselective iodination of  
39 aromatic compounds. The reaction is *para*-directed when possible. Otherwise, it  
40 occurs in the *ortho*-position. In addition, competitive experiments ( $k_{\text{mesitylene}}:k_{\text{durene}}$ )  
41 suggest a polar mechanism for this process, in agreement with the behavior in  
42 molecular solvents.

43 Fluoroarenes have also been obtained using [EMIM]<sup>+</sup> and [BMIM]<sup>+</sup> salts with  
44 [BF<sub>4</sub>]<sup>-</sup> and [PF<sub>6</sub>]<sup>-</sup> counteranions as solvents for fluorodediazotiation and for *in*  
45 *situ* diazotination with [NO][BF<sub>4</sub>] and [NO][PF<sub>6</sub>] [64]. It is generally agreed that

1 in conventional solvents fluorodediazotization occurs via a tight ion pair. In ionic  
2 liquids the diazonium salt is surely coordinated with one or more anions, how-  
3 ever, experiments carried out on  $[\text{ArN}_2][\text{BF}_4]$  in  $[\text{EMIM}][\text{CF}_3\text{CO}_2]$ ,  $[\text{EMIM}][\text{OTf}]$   
4 and  $[\text{EMIM}][\text{OTf}]$  show that in these media the ionic intermediates behave like  
5 "solvent-separated ion pairs." Only products arising from the ionic liquid anion  
6 quenching were obtained in all investigated ionic liquids, showing that on mixing  
7 metathesis occurs immediately. This behavior is in agreement with the data related  
8 to the glycosidation reaction [43], previously discussed.

9 Finally, it must be noted that the ionic liquid anion may have an active role  
10 in this kind of reaction, determining the outcome of some chemical reactions  
11 [65]. The reaction of toluene and nitric acid gives a nitrated product in triflate  
12 and hydrogensulfate ionic liquids, whereas the monohalogenated product can be  
13 obtained in a halide salt. On the other hand, nitric acid acts as an oxidizing agent  
14 in methansulfonate ionic liquids to give benzoic acid in quantitative yields. Ionic  
15 liquids seem to be able to catalyze these reactions with the only by-product being  
16 water.

#### 17 18 19 5.1.4

#### 20 Conclusions

21  
22 In this section, it has been highlighted that the use of ionic liquids as solvents  
23 for organic reactions is not merely an environmentally friendly alternative, but  
24 has considerable additional consequences on reactivity in the form of significant  
25 variations in reaction rates and selectivities.

26 The interactions between cations and anions render the ionic liquids highly or-  
27 dered three-dimensional supramolecular networks and the possibility for cations  
28 or anions to interact with dissolved species (reagents, intermediates or transition  
29 states) is a competitive process which depends on the relative strengths of the  
30 anion-cation and solute-anion (or cation) interactions. When the solute is able to  
31 give interactions that can compete with those present inside the ionic liquid, the  
32 latter behaves as a polar solvent. The high polarizability/dipolarity, generally char-  
33 acterizing these solvents, together with the ability of cation and anion to hydrogen  
34 bond, determines the solvation of substrates, transition states and intermediates,  
35 and therefore their reactivity in ionic liquids. Moreover, since ionic liquids are  
36 normally much more ordered solvents than molecular ones, the formation of the  
37 activated complex from the reagents may, at least partially, destroy the degree of  
38 order of the system, giving significant entropic contributions to the reactions per-  
39 formed in these media.

40 Other properties of ionic liquids (such as viscosity, degree of order and the cohe-  
41 sive pressure) must be considered carefully, however, when these salts are employed  
42 as solvents. The importance of these latter parameters, moreover, increases when  
43 the solutes (reagents and transition states) are not able to give competitive interac-  
44 tions with the components of the ionic liquid. In this situation, all the properties  
45 which determine the ionic liquid's polarity become unimportant, and the systems,

with the extensive association of their cations and anions, behave as non-polar solvents. The high cohesive pressure may favor associative processes, whereas the elevated viscosity may reduce the rate of diffusion-controlled reactions and very fast reactions may become controlled by the solvent re-orientation.

It is, however, notable that the strong attractive interactions between ions, which are at the origin of the tendency of ions to associate in ion aggregates, may determine the formation of cavities inside the IL. The presence of cavities may favor the motion of small, uncharged species and render ionic liquids in this situation much more similar to polymeric matrixes than to true solvents.

In conclusion, ionic liquids probably cannot be considered as polar solvents, nor as non-polar solvents, nor as polymeric matrixes. Their behavior arises from a fine balancing of entropic and enthalpic contributions that involve all of the interactions inside the ionic liquid and all of the possible interactions between cations and/or anions and dissolved species. The ability of ionic liquids to affect reactivity is, therefore, much more complicated to rationalize and more parameters must be considered to explain the "ionic liquid effect" on reaction rate and selectivity than with molecular solvents.

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## 292 | 5 Organic Synthesis

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## 5.2

## Stoichiometric Organic Reactions and Acid-catalyzed Reactions in Ionic Liquids

Martyn Earle

The field of reaction chemistry in ionic liquids was initially confined to the use of chloroaluminate(III) ionic liquids. With the development of “neutral” ionic liquids in the mid-1990s, the range of reactions that can be performed has expanded rapidly. In this section, reactions in both chloroaluminate(III) ionic liquids and similar Lewis acidic media are described. In addition, stoichiometric reactions, mostly in neutral ionic liquids, are discussed. Review articles are available by several authors, including Welton [1] (reaction chemistry in ionic liquids), Holbrey [2, 3] (properties and phase behavior), Earle [4] (reaction chemistry in ionic liquids), Rooney [5] (physical properties of ionic liquids), Seddon [6, 7] (chloroaluminate(III) ionic liquids and industrial applications), Wasserscheid [8] (catalysis in ionic liquids), Dupont [9, 10] (catalysis in ionic liquids) and Sheldon [11] (catalysis in ionic liquids).

1 Ionic liquids have been described as "Designer Solvents" [12]. Simply by making  
2 changes to the structure of either the anion, or the cation, or both, properties  
3 such as solubility, density, refractive index and viscosity can be adjusted to suit  
4 requirements [13, 14]. This degree of control can be of substantial benefit when  
5 carrying out solvent extractions or product separations, as the relative solubilities  
6 of the ionic and extraction phases can be adjusted to assist with the separation [15].  
7 Separation of the products can also be achieved by other means such as distillation  
8 (usually under vacuum), steam distillation and supercritical fluid extraction  
9 ( $\text{CO}_2$ ).

10 To many chemists, performing reactions in ionic liquids may seem daunting  
11 and the range of ionic liquids or potential ionic liquids available is very large.  
12 However, many have found that performing reactions in ionic liquids is straight-  
13 forward and practical, compared to similar reactions in conventional organic sol-  
14 vents. This is particularly the case when considering reactions normally carried out  
15 in noxious and difficult to remove solvents such as dipolar aprotic solvents like  
16 dimethylsulfoxide.

17 With the growing interest in ionic liquids, reactions were initially performed  
18 in various chloroaluminate(III) ionic liquids. Their strong solvating ability was an  
19 advantage, but their sensitivity to moisture and strong interactions with certain  
20 commonly occurring functional groups limited the scope of reactions in these me-  
21 dia. With the discovery of water-stable "neutral" ionic liquids, the range of reactions  
22 that can be performed has grown to cover most classes of reactions found in organic  
23 chemistry textbooks [16]. The vast majority of the reactions in ionic liquids are now  
24 carried out in these ionic liquids.

25 Chloroaluminate(III) ionic liquids are excellent media for many processes, but  
26 suffer from several disadvantages, such as their moisture sensitivity and the diffi-  
27 culty of separation of products containing heteroatoms. Furthermore, these ionic  
28 liquids often have to be quenched (usually in water) at the end of a chemical reac-  
29 tion, and are lost in the form of acidic aqueous waste. Hence research is shifting  
30 to the investigation of ionic liquids that are stable to water. This allows for straight-  
31 forward product separation and easier handling. In particular, a number of ionic  
32 liquids have been found to be hydrophobic (immiscible with water), but readily  
33 dissolve many organic molecules (with the exception of alkanes, some ethers and  
34 alkylated aromatic compounds such as toluene). An example of this is the ionic  
35 liquid 1-butyl-3-methylimidazolium hexafluorophosphate [BMIM][PF<sub>6</sub>] [17], which  
36 forms triphasic solutions with alkanes and water [18]. This multiphasic behavior has  
37 important implications for clean synthesis and is analogous to the use of fluorous  
38 phases in some chemical processes [19]. For example, a reaction can be performed  
39 in the ionic liquid, the products separated by distillation or steam stripping, and a  
40 by-product extracted with water or an organic solvent.

41 Most of the chemistry carried out in neutral ionic liquids has centered around  
42 the use of [BMIM][PF<sub>6</sub>] and [BMIM][BF<sub>4</sub>] as solvents. These two ionic liquids were  
43 chosen because they are relatively simple to prepare and purify and their properties  
44 are well understood. Unfortunately, these two ionic liquids are not ideal solvents for  
45 many chemical reactions that are carried out under acidic or basic conditions [20].

This is because  $[\text{PF}_6]^-$  and  $[\text{BF}_4]^-$  ions can hydrolyse under either acidic or basic conditions [21] and the  $[\text{BMIM}]^+$  cation is not stable under basic conditions and can form a highly reactive carbene [22]. Thus ionic liquids based on ammonium and other ions are superseding these ionic liquids [23, 24].

### 5.2.1

#### Electrophilic Reactions

Ionic liquids have proven to be excellent media for electrophilic reactions. Many of the first electrophilic reactions were carried out in chloroaluminate(III) salts<sup>1</sup> and other related binary salts. These often proceed smoothly to give products in good yield and selectivity, however, it should be noted that these salts are water sensitive and reaction must be carried out under dry conditions. These salts react with water to give hydrolysed aluminum(III) ionic species and HCl. When a reactant or product contains a heteroatomic functional group, such as a ketone, a strong aluminum(III) chloride adduct is formed. In these cases, this adduct can be difficult to separate from the ionic liquid at the end of a reaction. The isolation of the product often involves destruction of the ionic liquid with water. For products that do not have polar electron-donating functional groups, isolation of the products is straightforward and the ionic liquid can be reused.

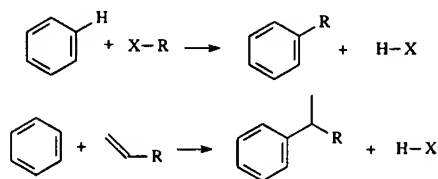
The disadvantages associated with the use of chloroaluminate(III) ionic liquids have led various authors to investigate alternative Lewis acidic ionic liquid media such as those based on zinc(II) chloride [25], tin(II) chloride [26] and indium(III) chloride [27]. These ionic liquids are considerably more water stable although much less reactive than the chloroaluminate(III) systems.

##### 5.2.1.1 Friedel-Crafts Reactions

The Friedel-Crafts reaction has been studied in detail by Olah [28, 29]. This reaction can be considered to be a reaction that results in the formation of carbon-carbon bonds that are "catalyzed" by either strong acids or Lewis acids. The term

<sup>1</sup> Chloroaluminate(III) salts belong to a class of ionic liquids called binary ionic liquids. The composition of a tetrachloroaluminate(III) ionic liquid is best described by the apparent mole fraction of  $\text{AlCl}_3$   $\{X(\text{AlCl}_3)\}$  present. Ionic liquids with  $X(\text{AlCl}_3) < 0.5$  contain an excess of  $\text{Cl}^-$  ions, and are called "basic"; those with  $X(\text{AlCl}_3) > 0.5$  contain an excess of  $[\text{Al}_2\text{Cl}_7]^-$  ions, and are called "acidic"; melts with  $X(\text{AlCl}_3) = 0.5$  are called 'neutral'. For example, the binary salt  $\text{NaCl-AlCl}_3$  ( $X = 0.67$ ) refers to a 1 part NaCl to 2 parts  $\text{AlCl}_3$  mixture of salts and is described as "acidic".

## 5.2 Stoichiometric Organic Reactions and Acid-catalyzed Reactions in Ionic Liquids | 295



Scheme 5.2-1 The Friedel-Crafts alkylation reaction (R = alkyl, X = leaving group) [29].

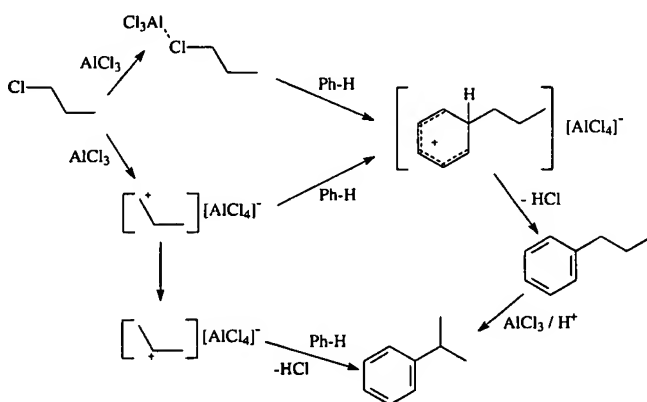
“catalyzed” is not always appropriate since, in many reactions, the so-called catalyst is a stoichiometric reagent.

### Friedel-Crafts alkylation reactions

The Friedel-Crafts alkylation reaction usually involves the interaction of an alkylating agent such as an alkyl halide, alcohol or alkene with an aromatic compound, to form an alkylated aromatic compound (Scheme 5.2-1).

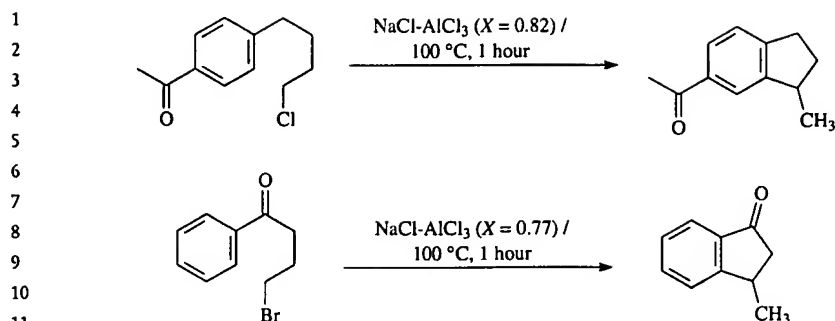
It should be noted that Scheme 5.2-1 denotes idealized Friedel-Crafts alkylation reactions. In practice, there are a number of problems associated with the reaction. These include polyalkylation reactions since the products of a Friedel-Crafts alkylation reaction are often more reactive than the starting material. Also isomerization and rearrangement reactions can occur, which can lead to a large number of products [28,29]. The mechanism of Friedel-Crafts reactions is not straightforward, and it is possible to propose two or more different mechanisms for a given reaction. Examples of the typical processes occurring in a Friedel-Crafts alkylation reaction are given in Scheme 5.2-2 for the reaction of 1-chloropropane and benzene.

The chemical behavior of acidic chloroaluminate(III) ionic liquids (where  $X(\text{AlCl}_3) > 0.50$ ) [6] is that of a powerful Lewis acid. As might be expected, it catalyzes reactions that are conventionally catalyzed by aluminum(III) chloride, without suffering the disadvantage of the low solubility of aluminum(III) chloride in many solvents.

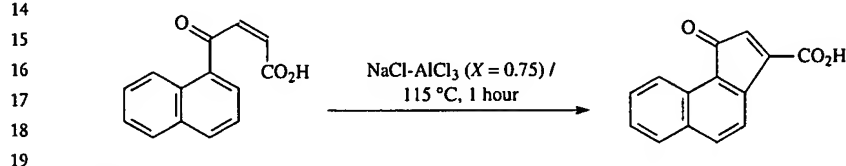


Scheme 5.2-2 The reaction of 1-chloropropane and benzene [29].

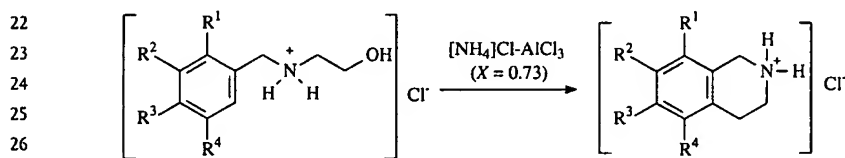
## 296 | 5 Organic Synthesis



Scheme 5.2-3 The intramolecular cyclization of alkyl chlorides and bromides [30].



Scheme 5.2-4 The intramolecular cyclization of an alkene in a molten salt [31].

Scheme 5.2-5 The cyclodehydration of *N*-benzylethanamine chloride [32].

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The first examples of alkylation reactions in “molten salts” were reported in the 1950s. Baddeley and Williamson performed a number of intramolecular cyclization reactions [30] (Scheme 5.2-3). These were carried out in mixtures of sodium chloride and aluminum chloride. The reactions were run at below the melting point of the salt, and it is presumed that the mixture of reagents acted to lower the melting point.

37

Baddeley also investigated the cyclization of alkenes in the NaCl-AlCl<sub>3</sub> molten salt. An example is given in Scheme 5.2-4 [31].

38

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41

Mendelson et al. [32] also investigated a number of cyclization reactions. One of these involved the cyclodehydration of *N*-benzylethanamine chloride in a molten salt derived from AlCl<sub>3</sub> and NH<sub>4</sub>Cl ( $X = 0.73$ ). This gave rise to the corresponding tetrahydroisoquinoline in 41–80% yield, as shown in Scheme 5.2-5.

42

43

44

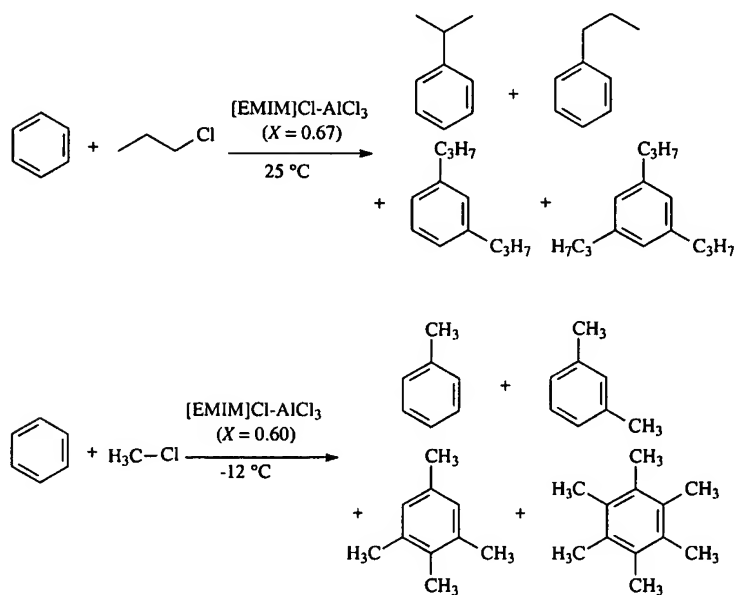
45

Boon et al. investigated the reactions of benzene and toluene in room-temperature ionic liquids based on [EMIM]Cl-AlCl<sub>3</sub> mixtures [33]. The reactions of various alkyl chlorides with benzene in the ionic liquid [EMIM]Cl-AlCl<sub>3</sub> ( $X = 0.60$  or  $0.67$ ) was carried out and the product distribution is given in Table 5.2-1 and Scheme 5.2-6.

## 5.2 Stoichiometric Organic Reactions and Acid-catalyzed Reactions in Ionic Liquids 297

Table 5.2-1 The products from the reactions of alkyl chlorides with benzene in [EMIM]Cl-AlCl<sub>3</sub> (X = 0.60 or 0.67) [33].

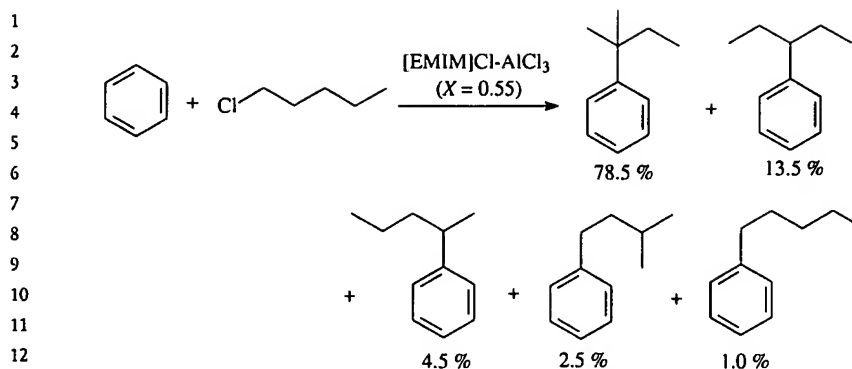
R-Cl	X	R-Cl:C <sub>6</sub> H <sub>6</sub> : IL	mono-	di-	tri-	tetra-	penta-	hexa-
methyl <sup>a</sup>	0.67	xs:1:1	1.5	58.5	1.5	26.8	1.4	10.2
ethyl <sup>a</sup>	0.67	xs:1:1	11.5	10.8	33.4	24.4		1.5
n-propyl <sup>b</sup>	0.60	1.25:1.25:1	24.8	19.9	55.3			
n-butyl <sup>b,c</sup>	0.60	1.33:1.33:1	25.0	26.3	48.7			
cyclohexyl	0.60	10:10:1	35.0	30.0	34.4			
benzyl <sup>d</sup>	0.60	0.78:1.17:1	50.0	34.5	15.6			

<sup>a</sup> At reflux temperature of alkyl halide.<sup>b</sup> Room temperature in dry box.<sup>c</sup> Only *sec*-butyl products formed.<sup>d</sup> Tar formed, only a small amount of alkylated product isolated.

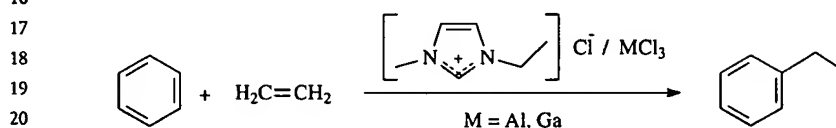
Scheme 5.2-6 The alkylation of benzene with methyl chloride or n-propyl chloride in an ionic liquid [33].

The methylation of benzene with methyl chloride proceeds to give predominantly dimethylbenzene (xylenes) and tetramethylbenzene, with about 10% hexamethylbenzene. In the propylation of benzene with 1-chloropropane, not only does polyalkylation occur, but there is also a considerable degree of isomerization of the n-propyl group to the isopropyl isomer (Scheme 5.2-6). In the butylation, complete isomerization of the butyl side chain occurs to give only *sec*-butyl benzenes.

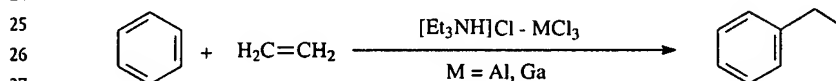
## 298 | 5 Organic Synthesis



15 **Scheme 5.2-7** The reaction of 1-chloropentane with benzene in  
16  $[\text{EMIM}]\text{Cl}-\text{AlCl}_3$  ( $X = 0.55$ ) [34].



23 **Scheme 5.2-8** The alkylation of aromatic compounds in  
24 chloroaluminate(III) or chlorogallate(III) ionic liquids [35].



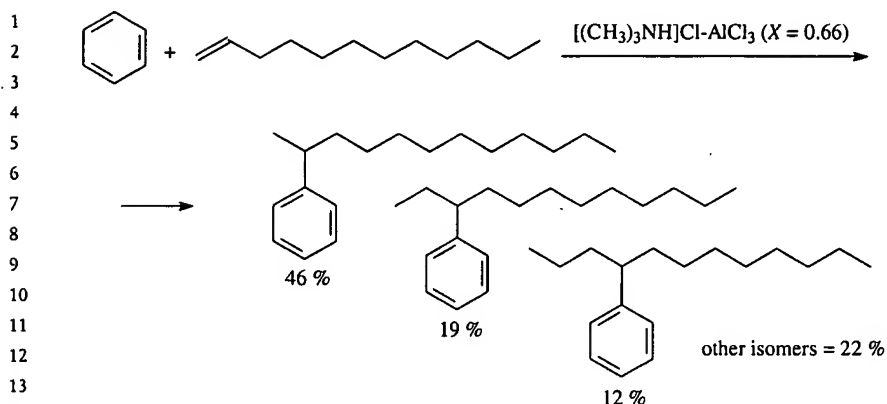
29 **Scheme 5.2-9** The reaction of benzene with ethylene in a triethylammonium ionic liquid [36].

31 Piersma and Merchant have studied the alkylation of benzene with various  
32 chloropentanes in  $[\text{EMIM}]\text{Cl}-\text{AlCl}_3$  ( $X = 0.55$ ) [34]. The reaction of 1-chloropentane  
33 with benzene gave a mixture of products, with surprisingly only a 1% yield of the  
34 unisomerized n-pentylbenzene. The major products of the reaction had all under-  
35 gone isomerization (Scheme 5.2-7).

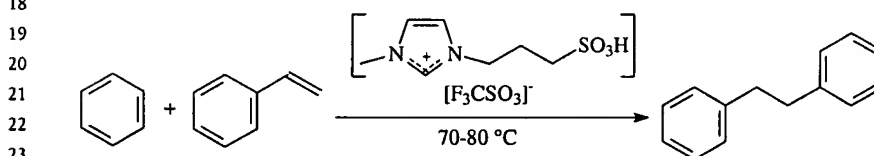
36 The details of two related patents for the alkylation of aromatic compounds with  
37 chloroaluminate(III) or chlorogallate(III) ionic liquid catalysts have become available.  
38 The first by Seddon and coworkers [35] describes the reaction of ethylene with ben-  
39 zene to give ethylbenzene (Scheme 5.2-8). This is carried out in an acidic ionic liquid  
40 based on an imidazolium cation and is claimed for ammonium, phosphonium and  
41 pyridinium cations. The anion exemplified in the patent is a chloroaluminate(III)  
42 and the claim includes for chlorogallate(III) anions and various mixtures of anions.

43 The second patent by Wasserscheid and coworkers [36] also describes the reaction  
44 of benzene with ethylene in ionic liquids, but exemplifies a different ionic liquid  
45 that is suitable for this reaction (Scheme 5.2-9).





15 **Scheme 5.2-10** The reaction of dodec-1-ene with benzene using an ionic  
16 liquid as a catalyst [37].

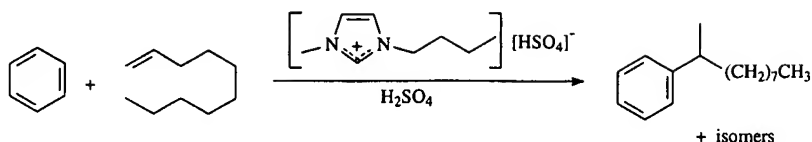


25 **Scheme 5.2-11** The task specific ionic liquid catalyzed alkylation of benzene [42].

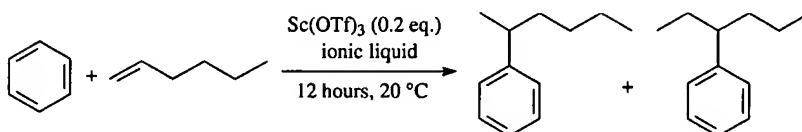
26  
27  
28 The production of linear alkyl benzenes (LABs) is carried out on a large scale for  
29 the production of surfactants. The reaction involves the reaction of benzene with a  
30 long chain alkene such as dodec-1-ene and often gives a mixture of isomers. Greco  
31 et al. have used a chloroaluminate(III) ionic liquid as a catalyst in the preparation of  
32 LABs [37] (Scheme 5.2-10).

33 Johnson and coworkers used two different chloroaluminate(III) ionic liquids  
34  $[\text{PyH}]\text{Cl}-\text{AlCl}_3$  or  $[(\text{C}_2\text{H}_5)_3\text{S}]\text{Br}-\text{AlCl}_3$  [38] in the alkylation of benzene with 1-  
35 pentene, 2-pentene and 1-octene and obtained the expected monoalkylbenzene  
36 when using a high alkene to benzene ratio. Disubstituted and rearrangement prod-  
37 ucts as well as dimerization and oligomerization of the alkene were also found  
38 to occur in these reactions [39]. Friedel-Crafts alkylations of 2-methylnaphthalene  
39 with long-chain alkenes (mixed  $\text{C}_{11-12}$  olefins) in acidic  $[(\text{C}_2\text{H}_5)_3\text{HN}]\text{Cl}-\text{AlCl}_3$  ionic  
40 liquids modified with HCl gave the expected alkylmethylnaphthalene in up to  
41 90% conversion and up to complete selectivity. The influences of the type and  
42 dosage of catalysts, molar ratio of 2-methylnaphthalene to alkenes and solvent to  
43 2-methylnaphthalene, reaction temperature and time were also studied [40]. A task  
44 specific ionic liquid, first described by Davis [41] was used in the alkylation of  
45 benzene, toluene and xylene [42] with styrene. This is shown in Scheme 5.2-11.

## 300 | 5 Organic Synthesis



**Scheme 5.2-12** The sulfuric acid catalyzed alkylation of benzene in a hydrogensulfate ionic liquid [43].



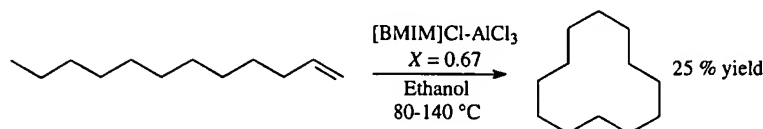
**Scheme 5.2-13** The alkylation of benzene with hex-1-ene catalyzed by scandium(III) triflate in ionic liquids [44].

Keim and coworkers have carried out various alkylation reactions of aromatic compounds in ionic liquids substantially free of Lewis acidity [43]. An example is the reaction of benzene with decene in  $[\text{BMIM}][\text{HSO}_4]$ , using sulfuric acid as the catalyst (Scheme 5.2-12). Keim has also claimed that these acid-ionic liquids systems can be used for esterification reactions.

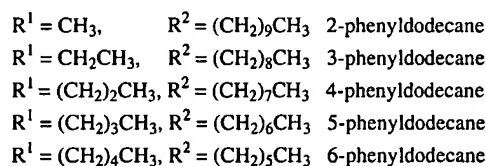
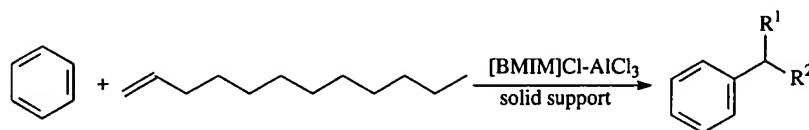
The Lewis acid dissolved in an ionic liquid methodology has been used for Friedel-Crafts alkylation reactions. Song [44] has reported that scandium(III) triflate in  $[\text{BMIM}][\text{PF}_6]$  acts as an alkylation catalyst in the reaction of benzene with hex-1-ene (Scheme 5.2-13).

The ionic liquids that were found to give the expected hexylbenzenes were  $[\text{BMIM}][\text{PF}_6]$ ,  $[\text{PMIM}][\text{PF}_6]$ ,  $[\text{HMIM}][\text{PF}_6]$ ,  $[\text{EMIM}][\text{SbF}_6]$  and  $[\text{BMIM}][\text{SbF}_6]$ . The reaction did not succeed in the corresponding tetrafluoroborate or trifluoromethanesulfonate ionic liquids. For the successful reactions, conversions of 99% of the hexene to products occurred, with 93–96% of the products being the monoalkylated product. The authors noted that the successful reactions all took place in the hydrophobic ionic liquids. It should be noted that the  $[\text{PF}_6]^-$  and  $[\text{SbF}_6]^-$  ions are less stable to hydrolysis reactions (resulting in the formation of HF) than the  $[\text{BF}_4]^-$  or  $[\text{OTf}]^-$  ions. The possibility of these reactions being catalyzed by traces of HF cannot be excluded [45]. Metal triflimide salts and bistrifluoromethanesulfonylimidic acid ( $\text{H}[\text{NTf}_2]$ ) dissolved in ionic liquids such as phosphonium triflimides [46] have also been found to catalyze the alkylation of benzene with alkenes [47].

The alkylation of phenol with *tert*-butyl alcohol was carried out in the ionic liquids  $[\text{BMIM}][\text{PF}_6]$  [48],  $[\text{C}_8\text{MIM}][\text{BF}_4]$ , and  $[\text{C}_6\text{MIM}][\text{BF}_4]$ . Comparative studies on the catalytic properties of ionic liquids,  $\text{H}_3\text{PO}_4$  and some solid acidic catalysts were carried out under identical reaction conditions, and the solvent effects were studied. The use of ionic liquids was found to enhance the catalytic properties of the catalysts used [49]. However, the claim that  $[\text{BMIM}][\text{PF}_6]$  alone can catalyze this reaction is uncertain, and, is probably due to the presence of traces of hydrogen fluoride in the ionic liquid [45, 46].  $\text{Dy}(\text{OTf})_3$  dissolved in various  $[\text{BF}_4]^-$  and  $[\text{PF}_6]^-$  ionic



Scheme 5.2-14 The cyclization of dodecene to cyclododecane [55].



Scheme 5.2-15 The alkylation of benzene with dodecene with an ionic liquid on a solid support [56, 57].

liquids has been used as a catalyst in the alkylation of indoles with ketones to form diindolylmethanes [50]. This reaction is also known to be Brønsted acid catalyzed [51]. A similar alkylation reaction using chloromethyl ether gave rise to a range of diaryl methanes [52] in a range of acidic chloroaluminate ionic liquids. The products were usually immiscible with the ionic liquids and could be easily separated, so that the ionic liquid could be reused.

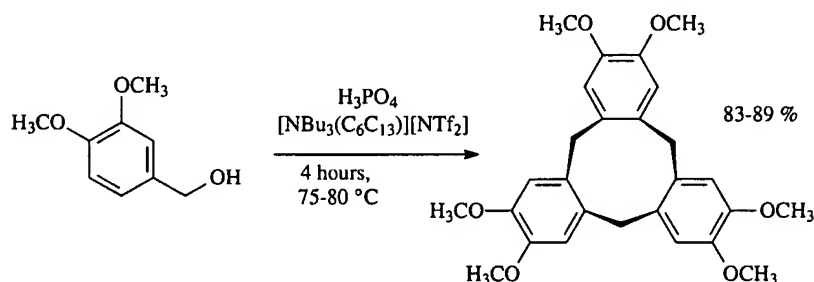
Alkylation of isobutane with 2-butene using various 1-alkyl-3-methylimidazolium halide–aluminum chloride catalysts has been successfully demonstrated [53]. Among these ionic liquids, [OMIM]Br–AlCl<sub>3</sub> displayed the best performance in terms of activity and selectivity for this reaction. From various parametric studies, such as anion compositions and temperature, optimum catalytic activity was observed at 80 °C and  $X = 0.52$ . This reaction has also been used to study the Lewis acidity of ionic liquids [54]. An interesting alkylation of an alkene can also be found in the cyclization of dodecene in a [BMIM]Cl–AlCl<sub>3</sub> ( $X = 0.67$ )/ethanol mixture at 6 MPa pressure (Scheme 5.2-14). The authors claim 27% yield and 93% selectivity for the formation of cyclododecane [55].

The alkylation of a number of aromatic compounds by the use of a chloroaluminate(III) ionic liquid on a solid support has been investigated by Hölderich and coworkers [56, 57]. Here the alkylation of aromatic compounds such as benzene, toluene, naphthalene and phenol with dodecene was performed using the ionic liquid [BMIM]Cl–AlCl<sub>3</sub> supported on silica, alumina and zirconia. With benzene, monoalkylated dodecylbenzenes were obtained (Scheme 5.2-15).

## 302 | 5 Organic Synthesis

Table 5.2-2 The product distribution dependence on the catalyst used for the reaction of benzene with dodecene. IL = [BMIM]Cl-AlCl<sub>3</sub> (X = 0.6), Temperature = 80 °C, with 6 mol% catalyst and benzene to dodecene ratio = 10:1.

Catalyst	2-Phenyl dodecane	3-Phenyl dodecane	4-Phenyl dodecane	5-Phenyl dodecane	6-Phenyl dodecane
AlCl <sub>3</sub>	46.4	19.4	12.7	12.1	9.5
IL (X = 0.6)	36.7	19.0	15.0	15.5	13.8
T 350/IL	42.9	22.8	13.0	11.8	9.4
H-Beta	75.7	19.0	3.8	1.1	0.4
H-Beta/IL	43.9	21.2	12.4	12.0	10.5

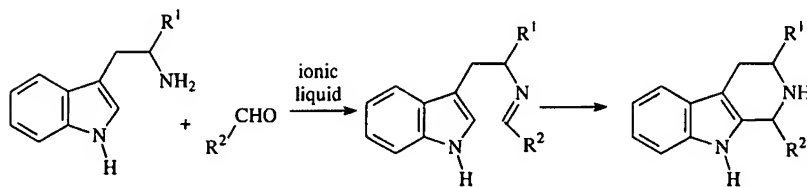


Scheme 5.2-16 The cyclization of 3,4-dimethoxyphenylmethanol in an ionic liquid [58].

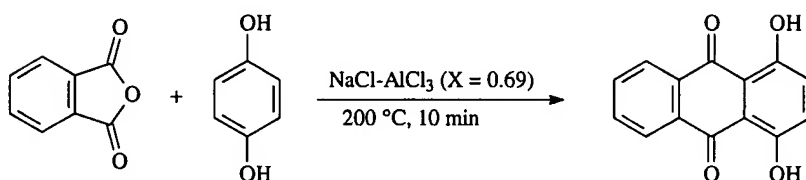
The product distribution in the reaction of benzene with dodecene was determined for a number of catalysts (Scheme 5.2-15, Table 5.2-2). As can be seen, the reaction with the zeolite H-Beta gave predominantly the 2-phenyldodecane whereas the reaction in the pure ionic liquid gave a mixture of isomers, with selectivity similar to that of aluminum chloride. The two supported ionic liquid reactions (H-Beta/IL and T 350/IL) gave product distributions again similar to aluminum(III) chloride (T350 is a silica support made by Degussa).

Raston has reported an acid catalyzed Friedel-Crafts reaction [58] where compounds such as 3,4-dimethoxyphenylmethanol were cyclized to cyclotrimeratrylene (Scheme 5.2-16). The reactions were carried out in tributylhexylammonium bistrifluoromethanesulfonylimide [NBu<sub>3</sub>(C<sub>6</sub>H<sub>13</sub>)] [NTf<sub>2</sub>] using a phosphoric or *p*-toluenesulfonic acid catalyst. The product was isolated by dissolving the ionic liquid/catalyst in methanol and filtering off the cyclotrimeratrylene product as white crystals. Evaporation of the methanol allowed the ionic liquid and catalyst to be regenerated.

The Pictet-Spengler reaction is a form of intermolecular Friedel-Crafts alkylation reaction. An example of this is the ionic liquid catalyzed and Lewis acid catalyzed one-pot Pictet-Spengler reactions of tryptophan methyl ester or tryptamine with aliphatic and aromatic aldehydes [59]. Short reaction times were achieved with the aid of microwave irradiation (Scheme 5.2-17).



Scheme 5.2-17 The Pictet-Spengler reaction in ionic liquids [59].



Scheme 5.2-18 The reaction of phthalic anhydride with hydroquinone in  $\text{NaCl-AlCl}_3$  ( $X = 0.69$ ) [60].

### Friedel-Crafts acylation reactions

Friedel-Crafts acylation reactions usually involve the interaction of an aromatic compound with an acyl halide or anhydride in the presence of a catalyst, to form a carbon-carbon bond [28]. As the product of an acylation reaction is less reactive than its starting material, usually monoacylation occurs. The “catalyst” in the reaction is not a true catalyst, as it is often (but not always) required in stoichiometric quantities. For Friedel-Crafts acylation reactions in chloroaluminate(III) ionic liquids or molten salts, the ketone product of an acylation reaction forms a strong complex with the ionic liquid, and separation of the product from the ionic liquid can be extremely difficult. The products are usually isolated by quenching the ionic liquid in water. Current research is moving towards finding genuine catalysts for this reaction, some of which are described in this section.

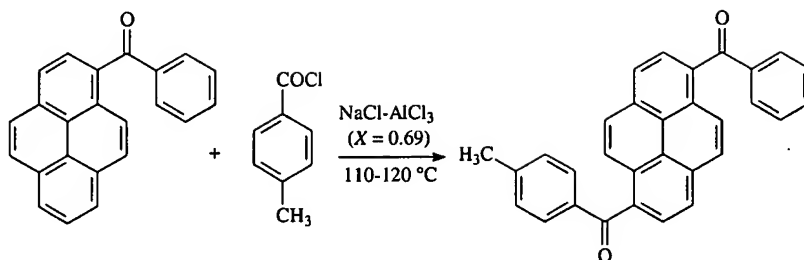
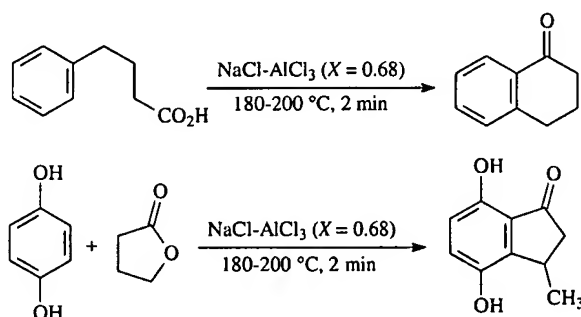
The first example of a Friedel-Crafts acylation reaction in a molten salt was carried out by Raudnitz and Laube [60]. This involved the reaction of phthalic anhydride with hydroquinone at 200 °C in  $\text{NaCl-AlCl}_3$  ( $X = 0.69$ ) (Scheme 5.2-18).

Scholl and coworkers [61] performed the acylation of 1-benzoylpyrene with 4-methylbenzoyl chloride in a  $\text{NaCl-AlCl}_3$  ( $X = 0.69$ ) molten salt (110–120 °C). This gave 1-benzoyl-6-(4-methylbenzoyl)pyrene as the major product (Scheme 5.2-19).

Bruce et al. carried out the cyclization of 4-phenylbutyric acid to tetralone in  $\text{NaCl-AlCl}_3$  ( $X = 0.68$ ) at 180–200 °C [62]. The reaction of valerolactone with hydroquinone was also performed by Bruce, to give 3-methyl-4,7-dihydroxyindanone using the same ionic liquid and reaction conditions. These reactions are shown in Scheme 5.2-20.

The Fries rearrangement can be considered to be a type of Friedel-Crafts acylation reaction. Two examples of this reaction are given in Scheme 5.2-21. The first is the

## 304 | 5 Organic Synthesis

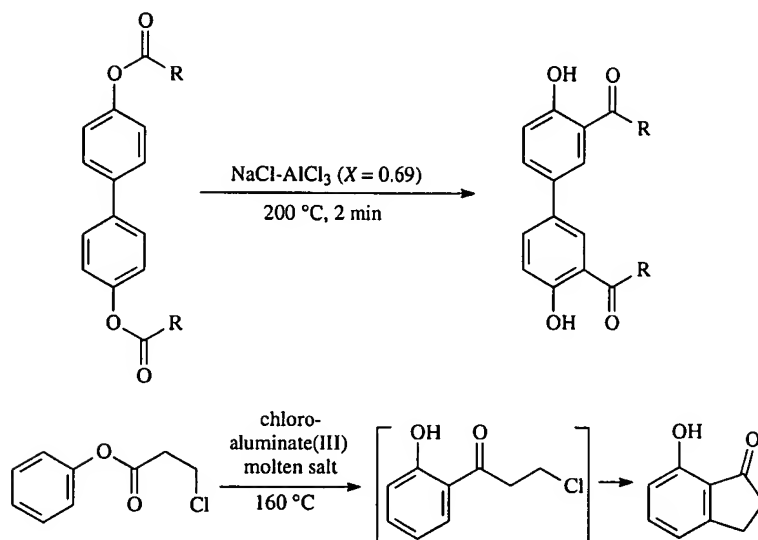
Scheme 5.2-19 The acylation of 1-benzoylpyrene in NaCl-AlCl<sub>3</sub> (X = 0.69) [61].Scheme 5.2-20 The use of NaCl-AlCl<sub>3</sub> (X = 0.68) in the formation of cyclic ketones [62].

rearrangement of 4,4'-diacetoxybiphenyl to 4,4'-dihydroxy-3,3'-diacetoxybiphenyl in a NaCl-AlCl<sub>3</sub> (X = 0.69) molten salt [63]. The second example is the rearrangement of phenyl 3-chloropropionate to 2'-hydroxy-3-chloropropiophenone followed by cyclization to an indanone [64].

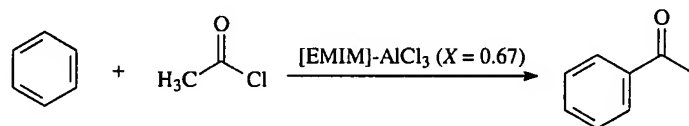
One of the problems with these NaCl-AlCl<sub>3</sub> molten salts is their high melting points and corresponding high reaction temperatures. The high reaction temperatures tend to cause side reactions and decomposition of the products of the reaction. Hence, a number of reactions were carried out under milder conditions, in room temperature ionic liquids. The first example of a Friedel-Crafts acylation in such an ionic liquid was performed by Wilkes and coworkers [33, 69] (Scheme 5.2-22).

The rate of the acetylation reaction was found to be dependent on the concentration of the [Al<sub>2</sub>Cl<sub>7</sub>]<sup>-</sup> ion and suggested that this ion was acting as the Lewis acid in the reaction. Wilkes goes on to provide evidence that the acylating agent is the acetylium ion [H<sub>3</sub>CCO]<sup>+</sup> [33, 65].

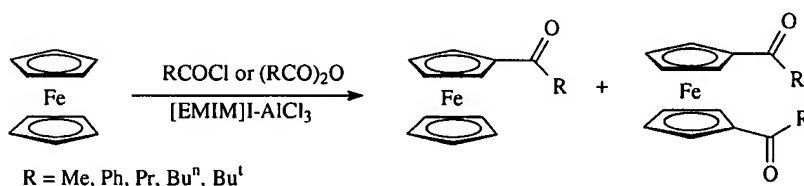
Singer and coworkers have investigated the acylation reactions of ferrocene in ionic liquids made from mixtures of [EMIM]I and aluminum(III) chloride [66, 67]. They found that in the basic or neutral [EMIM]I-AlCl<sub>3</sub> (X < 0.50) no reaction occurred. In mildly acidic [EMIM]I-AlCl<sub>3</sub>, the mono-acetylated ferrocene was obtained as the major product. In strongly acidic [EMIM]I-AlCl<sub>3</sub> (X = 0.67) the diacylated



**Scheme 5.2-21** The Fries rearrangement in chloroaluminate(III) molten salts [63, 64].



**Scheme 5.2-22** The acetylation of benzene in a room temperature ionic liquid [65].

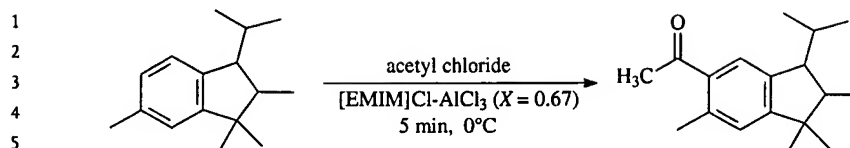


**Scheme 5.2-23** The acylation of ferrocene in  $[\text{EMIM}]\text{-AlCl}_3$  [66, 67].

ferrocene was the major product. Also, when  $\text{R} = \text{alkyl}$ , the diacylated product was usually the major product, but for  $\text{R} = \text{Ph}$ , the monoacylated product was favored (Scheme 5.2-23).

A number of commercially important fragrance molecules have been synthesised by Friedel-Crafts acylation reactions in these ionic liquids. Traseolide<sup>®</sup> (5-acetyl-1,1,2,6-tetramethyl-3-isopropylindane) (Scheme 5.2-24) has been made in high yield in the ionic liquid  $[\text{EMIM}]\text{Cl-AlCl}_3$  ( $X = 0.67$ ). For the acylation of naphthalene, the ionic liquid gives the highest reported selectivity for the 1-position

## 306 | 5 Organic Synthesis



**Scheme 5.2-24** The acetylation of 1,1,2,6-tetramethyl-3-isopropylindane in [EMIM]Cl-AlCl<sub>3</sub> (X = 0.67) [68].

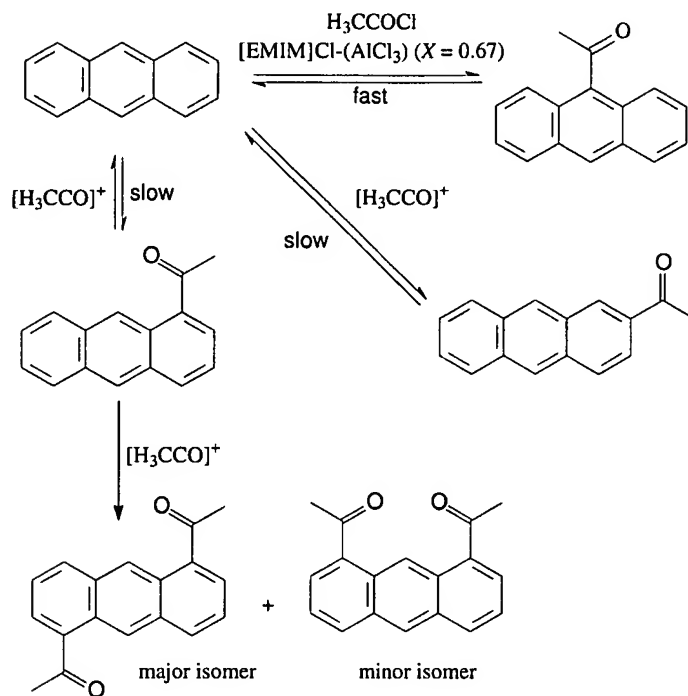
[68]. The acetylation of anthracene at 0 °C was found to be a reversible reaction. The initial product of the reaction of acetyl chloride (1.1 equivalents) with anthracene is 9-acetylanthracene, formed in 70% yield in less than 5 min. The 9-acetylanthracene was then found to undergo diacetylation reactions, giving the 1,5- and 1,8-diacetylanthracene and anthracene after 24 h (Scheme 5.2-25). This was confirmed by taking a sample of 9-acetyl anthracene and allowing it to isomerize in the ionic liquid. This gave a mixture of anthracene, 1,5-diacetylanthracene and 1,8-diacetylanthracene. It should be noted that a proton source was needed for this reaction to occur, implying an acid catalyzed mechanism (Scheme 5.2-26) [68]. Acylation as well as dealkylation reactions have been performed by Gigante et al. in 1-alkyl-3-methylimidazolium ionic liquid–aluminum(III) chloride mixtures, on methyl dehydroabietate (Fig. 5.2-1) [69]. When contacted with the ionic liquid in the presence of toluene, the isopropyl group was transferred to the toluene. When acetyl chloride was added, acylation took place *ortho*- to the isopropyl group in up to 97% yield. Similar deacylation and transacylation reactions have been observed by Laali and Sarca in the reactions of 2,4,6-trimethylacetophenone and pentamethylacetophenone in various triflate, tetrafluoroborate and hexafluorophosphate ionic liquids [70].

Metal triflimide salts were found to be excellent catalysts for Friedel-Crafts acylation reactions of aromatic compounds [47, 71]. Although these salts will catalyze the reaction by themselves, their reactivity is increased significantly when dissolved in triflimide ionic liquids, and the ionic liquid/catalyst can be recycled [71]. Surprisingly, the metal triflimides with the greatest activity were those of cobalt(II), nickel(II), manganese(II), iron(III) and indium(III) (Scheme 5.2-27).

Wasserscheid et al. found that aluminum chloride dissolves in triflimide ionic liquids to form biphasic solutions. These solutions can be used to promote the Friedel-Crafts acylation reaction, and an interesting variant is the carbonylation of toluene with carbon monoxide (Scheme 5.2-28) [72]. The ionic liquid can be recycled, but the aluminum chloride is lost when the reaction is worked up.

The Friedel-Crafts acylation reaction has also been performed in iron(III) chloride ionic liquids by Seddon and coworkers [73]. An example is the acetylation of benzene (Scheme 5.2-29). The ionic liquids of the type: [EMIM]Cl-FeCl<sub>3</sub> (0.50 < X < 0.62) are good acylation catalysts, with the added benefit that the ketone product of the reaction can be separated from the ionic liquid by solvent extraction, provided that X is in the range 0.51–0.55. An improvement on the iron(III) binary ionic liquids



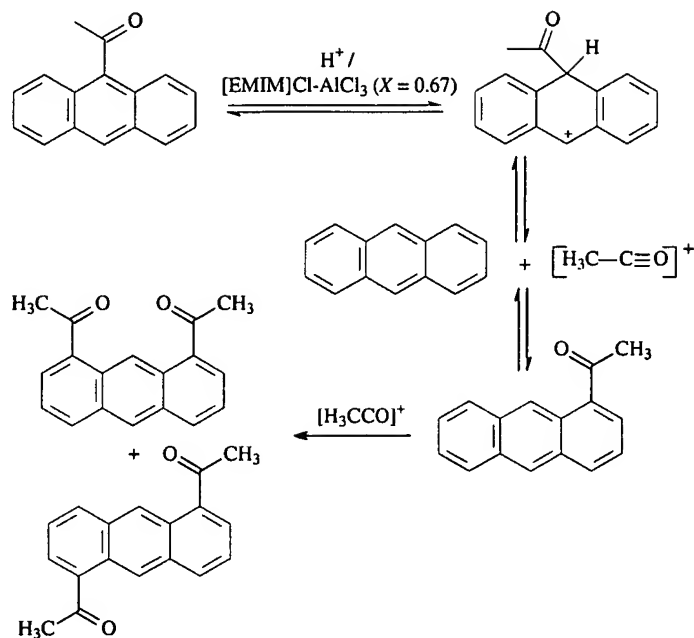


Scheme 5.2-25 The acetylation of anthracene in  $[\text{EMIM}]\text{Cl}-\text{AlCl}_3$  ( $X = 0.67$ ) [68].

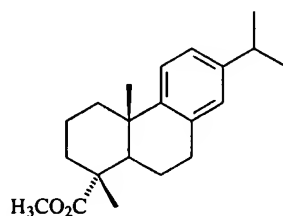
is the use of indium(III) chloride ionic liquids in the catalytic acylation of aromatic compounds [74]. Although this is less reactive than the iron(III) system, it has the advantage that the ionic liquid is water stable, and the ionic liquid can be recycled by washing the product with water to dissolve the indium ionic liquid, followed by evaporation of the water to regenerate the ionic liquid [75].

The ability of iron(III) chloride to genuinely catalyze Friedel-Crafts acylation reactions has also been recognized by Hölderich and coworkers [76]. By immobilizing the ionic liquid  $[\text{BMIM}]\text{Cl}-\text{FeCl}_3$  on a solid support Hölderich was able to acetylate mesitylene, anisole and *m*-xylene with acetyl chloride in excellent yield. The performance of the iron-based ionic liquid was then compared with the corresponding chlorostannate(II) and chloroaluminate(III) ionic liquids. The results are given in Scheme 5.2-30 and Table 5.2-3. As can be seen, the iron catalyst gave superior results to the aluminum or tin-based catalysts. The reactions were also carried out in the gas phase at between 200 and 300 °C. The acylation reaction was complicated by two side reactions. For example, in the reaction of acetyl chloride with *m*-xylene, the decomposition of acetyl chloride to ketene and the formation of 1-(1-chlorovinyl)-2,4-dimethylbenzene were also found to occur [76].

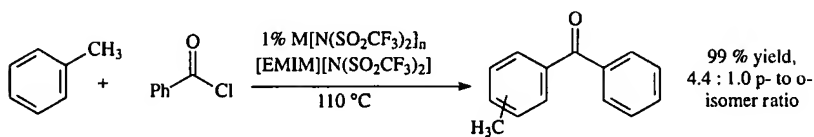
## 308 | 5 Organic Synthesis



**Scheme 5.2-26** Proposed mechanism for the isomerization of 9-acetylanthracene in  $[\text{EMIM}]\text{Cl}-\text{AlCl}_3$  ( $X = 0.67$ ) [68].



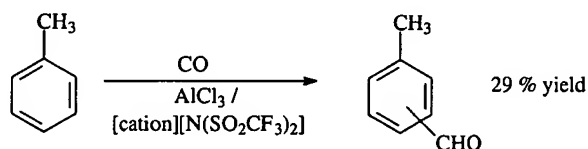
**Fig. 5.2-1** The structure of methyl dehydroabietate [69].



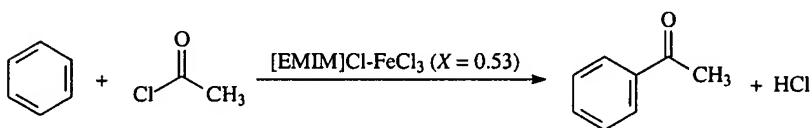
**Scheme 5.2-27** Metal triflimides as Friedel-Crafts acylation catalysts [47, 71].

Table 5.2-3 The acylation of aromatics in batch reactions at 100 °C, for 1 h. Ratio of aromatic compound to acetylating agent = 5:1. mes. = mesitylene.

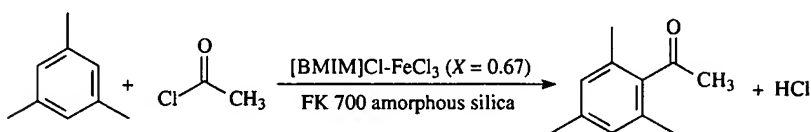
Ionic liquid	Reaction	Molar ratio IL:Ar-H	Conversion (%)	Selectivity (%)
[BMIM]Cl-AlCl <sub>3</sub>	mes. + AcCl	1:205	68.1	98
[BMIM]Cl-AlCl <sub>3</sub>	anisole + Ac <sub>2</sub> O	1:45	8.3	96
[BMIM]Cl-AlCl <sub>3</sub>	<i>m</i> -xylene + AcCl	1:205	3.5	96
[BMIM]Cl-FeCl <sub>3</sub>	mes. + AcCl	1:205	94.7	95
[BMIM]Cl-FeCl <sub>3</sub>	anisole + Ac <sub>2</sub> O	1:45	100	98
[BMIM]Cl-FeCl <sub>3</sub>	<i>m</i> -xylene + AcCl	1:205	33.8	79
[BMIM]Cl-SnCl <sub>2</sub>	anisole + Ac <sub>2</sub> O	1:45	19.7	94
[BMIM]Cl-SnCl <sub>2</sub>	<i>m</i> -xylene + AcCl	1:205	3.6	95



Scheme 5.2-28 The carbonylation of toluene in [cation][N(SO<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>]-AlCl<sub>3</sub> [72].



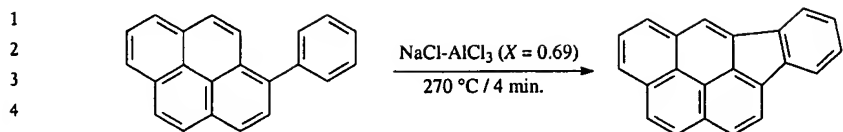
Scheme 5.2-29 The acetylation of benzene in an iron(III) chloride-based ionic liquid [73].



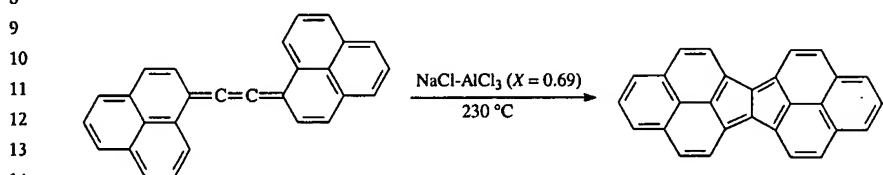
Scheme 5.2-30 The acetylation of aromatics with supported ionic liquids [76] (FK 700 is a type of amorphous silica made by Degussa).

Rebeiro and Khadilkar have investigated the reactions of trichloroalkanes with aromatic compounds. For example, the benzoylation of aromatic compounds in ionic liquids was performed using benzotrichloride, which on aqueous work up gave ketones [77]. Thioamidation of aromatic compounds can be achieved by the reaction of isothiocyanates with aromatic compounds in the presence of chloroaluminate ionic liquids [78].

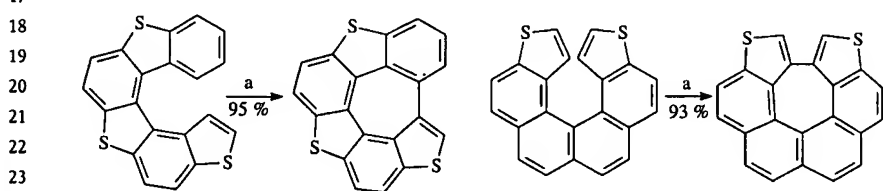
## 310 | 5 Organic Synthesis



6 **Scheme 5.2-31** The Scholl reaction of 1-phenylpyrene [79].



15 **Scheme 5.2-32** The cyclization of an aromatic cumulene in a molten salt [80].



25 **Scheme 5.2-33** The Scholl reactions of two helicenes. (a = NaCl-AlCl<sub>3</sub> ( $X$   
26 = 0.69) at 140 °C) [81].

### 27 5.2.1.2 Scholl and Related Reactions

28

29 One of the first reactions to be carried out in a molten salt (albeit at 270 °C) was

30 the Scholl reaction. This involves the inter- or intra-molecular coupling of two

31 aromatic rings. An example of this reaction is given in Scheme 5.2-31, where 1-

32 phenylpyrene was cyclized to indeno[1,2,3-cd]pyrene [79]. A more elaborate version

33 of the Scholl reaction is shown in Scheme 5.2-32 and involves bicyclization of an

34 aromatic cumulene [80].

35 Wynberg et al. found that the yields in the cyclization of helicenes could be

36 improved from 10% in an aluminum(III) chloride solution in benzene system

37 to 95% in a NaCl-AlCl<sub>3</sub> ( $X = 0.69$ ) molten salt [81]. An example is given in

38 Scheme 5.2-33.

39 The Scholl reaction involves an overall oxidation of the coupled aromatic rings,

40 yet, there is no obvious oxidizing agent. This leads to the question: what happens to

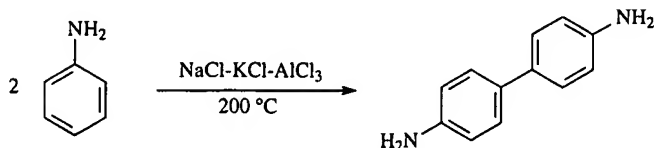
41 the two hydrogen atoms that are produced in this reaction? It has been suggested

42 that oxygen (air) may act as the oxidant but this currently lacks confirmation [82].

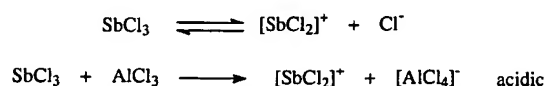
43 The molten salt NaCl-KCl-AlCl<sub>3</sub> (20:20:60) was used in the dimerization of aniline

44 to benzidine (Scheme 5.2-34) [83].

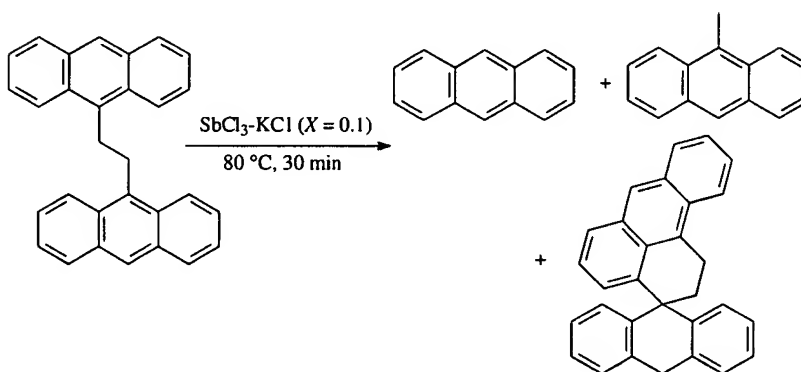
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Scheme 5.2-34 The oxidation of aniline to benzidine in a molten salt [83].



Scheme 5.2-35 The effect of adding aluminum(III) chloride to antimony(III) chloride [84, 85].



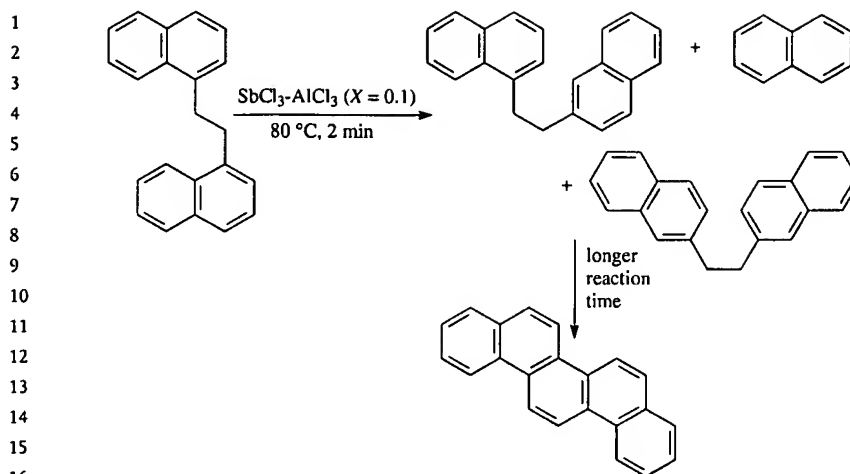
Scheme 5.2-36 The cyclization of 1,2-di-(9-anthryl)ethane in antimony(III) chloride ionic liquids [85].

Buchanan and coworkers studied the behavior of various aromatic compounds in antimony(III) chloride molten salts [84]. These salts can both act as a mild Lewis acid and allow redox reactions to take place. The Lewis acidity of the melt can be tuned by controlling the concentration of  $[\text{SbCl}_2]^+$  in the melts. Basic melts are formed by adding a few mol% of a chloride donor such as KCl, whereas acidic melts are formed by adding chloride acceptors such as  $\text{AlCl}_3$  (Scheme 5.2-35).

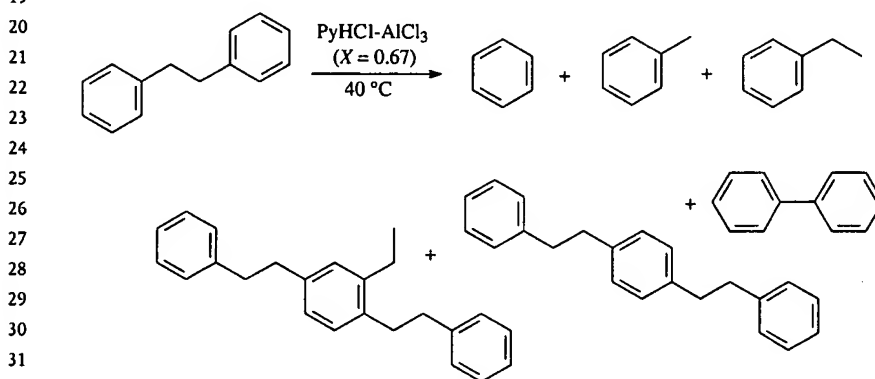
Examples of reactions that have been carried out in these antimony(III) chloride ionic liquids include the cyclizations of 1,2-di-(9-anthryl)ethane (Scheme 5.2-36) and 1,2-di-(1-naphthyl)ethane (Scheme 5.2-37). A more detailed review of the antimony(III) chloride molten salt chemistry has been published by Pagni [85].

In an attempt to study the behavior and chemistry of coal in ionic liquids, 1,2-diphenylethane was chosen as a molecule to model its chemical reactions. Newman et al. [86] investigated the behavior of 1,2-diphenylethane in acidic pyridinium chloroaluminate(III) melts ( $[\text{PyH}]\text{Cl}-\text{AlCl}_3$ ). At 40 °C, 1,2-diphenylethane undergoes

## 312 | 5 Organic Synthesis



Scheme 5.2-37 The reaction of dinaphthylethane in antimony(III) chloride ionic liquids [85].

Scheme 5.2-38 The reaction of 1,2-diphenylethane with  $[\text{PyH}]\text{Cl-AlCl}_3$  ( $X = 0.67$ ) [86].

a series of alkylation and dealkylation reactions to give a mixture of products. Some of the products are shown in Scheme 5.2-38. Newman also investigated the reactions of 1,2-diphenylethane with acylating agents such as acetyl chloride or acetic anhydride in the pyridinium ionic liquid [87] and with alcohols such as isopropanol [88].

## 5.2.1.3 Cracking and Isomerization Reactions

Cracking and isomerization reactions occur readily in acidic chloroaluminate(III) ionic liquids. A remarkable example of this is the reaction of polyethylene, which is converted to a mixture of gaseous alkanes with the formula  $(\text{C}_n\text{H}_{2n+2})$ , where

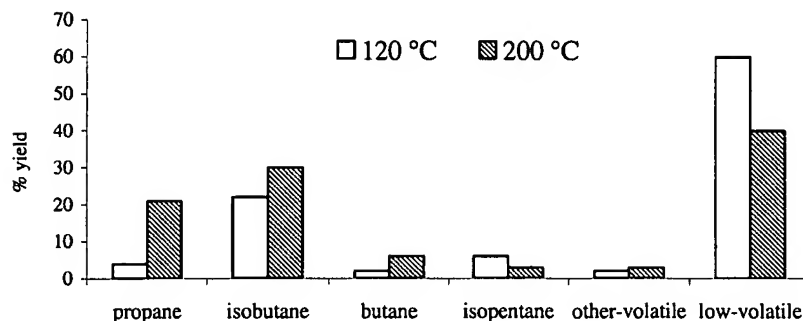
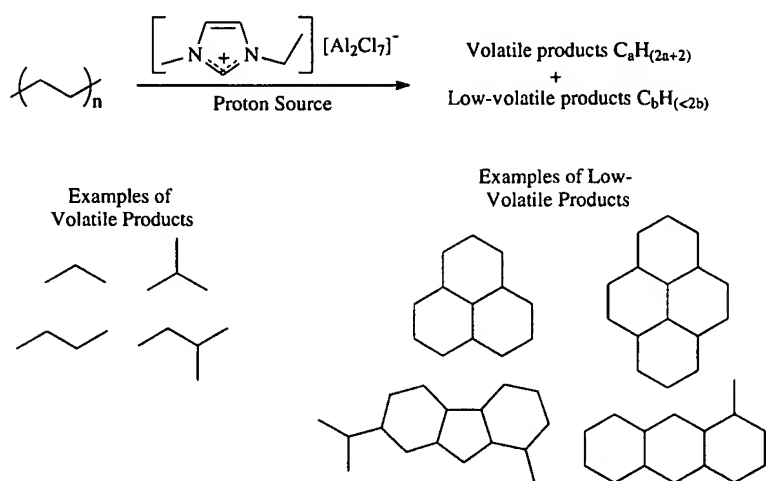


Fig. 5.2-2 The products from the ionic liquid cracking of high-density polyethylene at 120 °C and 200 °C [89].

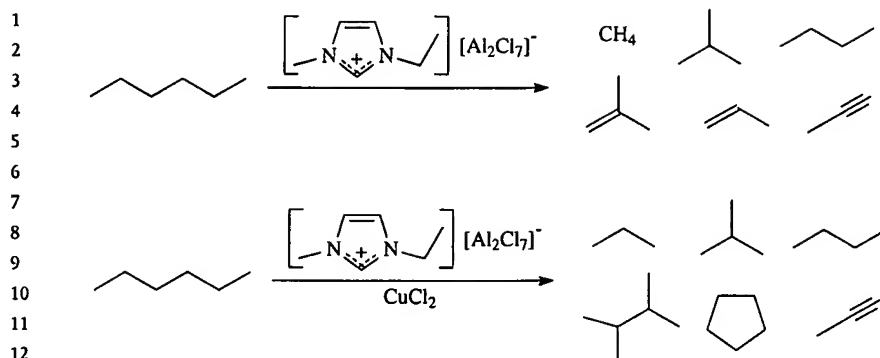
$n = 3-5$ ) and cyclic alkanes with a hydrogen to carbon ratio of less than two (Fig. 5.2-2, Scheme 5.2-39) [89].

The distribution of the products obtained from this reaction depends upon the reaction temperature (Fig. 5.2-2) and differs from other polyethylene recycling reactions in that aromatics and alkenes are not formed in significant concentrations. Another significant difference is that this ionic liquid reaction occurs at temperatures as low as 90 °C, whereas conventional catalytic reactions require much higher temperatures, typically 300–1000 °C [90]. A patent filed under the Secretary of State for Defence (UK) has reported a similar cracking reaction for lower molecular weight hydrocarbons in chloroaluminate(III) ionic liquids [91]. An example is the cracking of hexane to products like propene and isobutene (Scheme 5.2-40). The reaction was



Scheme 5.2-39 The cracking of polyethylene in an ionic liquid [89].

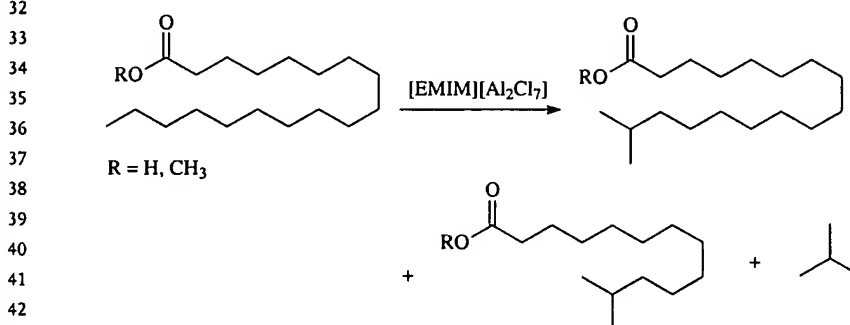
## 314 | 5 Organic Synthesis



**Scheme 5.2-40** The cracking of hexane in [EMIM]Cl–AlCl<sub>3</sub> ( $X = 0.67$ ) with and without added copper(II) chloride [91].

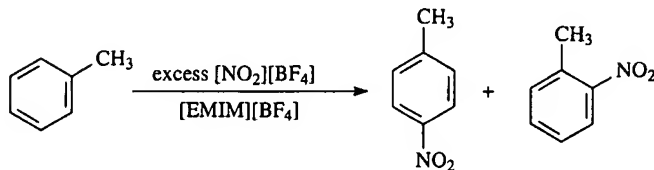
also performed with added copper(II) chloride, which gave a significantly different product distribution.

Johnson and coworkers investigated the cracking and isomerization of various alkanes such as nonane, tetradecane and 2-methylpentane in acidic pyridinium chloride–aluminum chloride ionic liquids. Similar product types to the cracking of hexane (above) were observed and after 15 days some polymerization of the cracked products had occurred [91]. A similar reaction occurs with fatty acids (such as stearic acid) or methyl stearate, which undergo isomerization, cracking, dimerization, and oligomerization reactions. This has been used to convert solid stearic acid into the more valuable liquid isostearic acid [92] (Scheme 5.2-41). The isomerization and dimerization of oleic acid and methyl oleate have also been found to occur in chloroaluminate(III) ionic liquids [93].



**Scheme 5.2-41** The cracking and isomerization of fatty acids and fatty acid methyl esters in chloroaluminate(III) ionic liquids [92, 93].





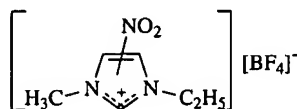
**Scheme 5.2-42** The nitration of toluene with  $[\text{NO}_2][\text{BF}_4]$  in  $[\text{EMIM}][\text{BF}_4]$  [95].

#### 5.2.1.4 Electrophilic Nitration Reactions

The first example of an electrophilic nitration in an ionic liquid was performed by Wilkes and coworkers [94]. Here a number of aromatic compounds were nitrated using  $\text{KNO}_3$  dissolved in chloroaluminate(III) ionic liquids. A number of nitration reactions have also been carried out by Laali et al. [95]. The reactions of nitrates, preformed nitronium salts and alkyl nitrates with aromatic compounds were performed in a wide range of ionic liquids. For example, the reaction of toluene with  $[\text{NO}_2][\text{BF}_4]$  in  $[\text{EMIM}]\text{Cl}$ ,  $[\text{EMIM}][\text{AlCl}_4]$ ,  $[\text{EMIM}][\text{Al}_2\text{Cl}_7]$ ,  $[\text{EMIM}][\text{BF}_4]$ ,  $[\text{EMIM}][\text{PF}_6]$ , and  $[\text{EMIM}][\text{OTf}]$  were all performed with varying degrees of success. Of these, the reaction in  $[\text{EMIM}][\text{BF}_4]$  (Scheme 5.2-42) gave the best yield (71%, 1.17 *o* : *p*-ratio), but only after the imidazolium ring had undergone nitration (Fig. 5.2-3).

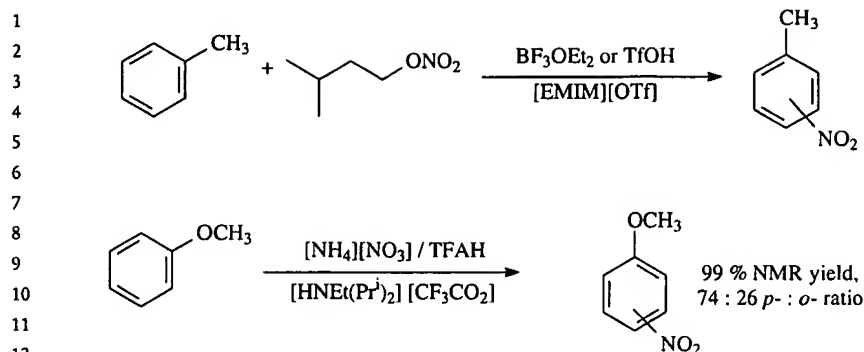
Other methods of nitration that Laali investigated used isoamyl nitrate combined with a Brønsted or Lewis acid in several ionic liquids, with  $[\text{EMIM}][\text{OTf}]$  giving the best yields (69%, 1.0:1.0 *o* : *p*-ratio). In the ionic liquid  $[\text{HNEt}(\text{Pr}^i)_2][\text{CF}_3\text{CO}_2]$  (m.p. = 92–93 °C) toluene was nitrated with a mixture of  $[\text{NH}_4][\text{NO}_3]$  and trifluoroacetic acid (TFAH) (Scheme 5.2-43). This gave ammonium trifluoroacetate  $[\text{NH}_4][\text{TFA}]$  as a by-product, which could be removed from the reaction vessel by distillation (sublimation).

The nitration of aromatic compounds with nitric acid in an ionic liquid was shown by Earle et al. [96, 97]. It was found that triflate and triflimide ionic liquids catalyze nitration reactions with nitric acid. This methodology has the advantage that water is the only by-product (Scheme 5.2-44). This process could also be carried out in phosphonium ionic liquids [46]. Acidic ionic liquids such as  $[\text{EMIM}][\text{HSO}_4]$  or the Davis-type ionic liquids [41] could also be used but gave lower reaction rates and selectivities [98]. The effect of metal triflates such as  $\text{Yb}(\text{OTf})_3$  or  $\text{Cu}(\text{OTf})_2$  dissolved in *N*-butyl-*N*-methylpyrrolidinium[triflimide] was investigated by Handy and Egrie [99]. These gave similar yields and selectivities to ionic liquids systems

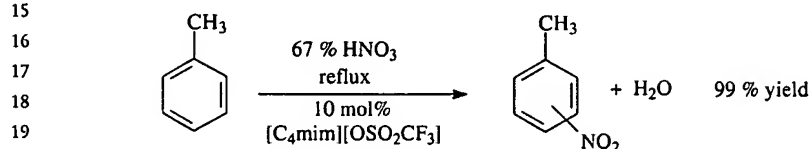


**Fig. 5.2-3** The structure of the nitroimidazolium ionic liquid [95].

## 316 | 5 Organic Synthesis



Scheme 5.2-43 Aromatic nitration reactions in ionic liquids [95].



Scheme 5.2-44 The nitration of aromatic compounds in triflate ionic liquids [96, 97].

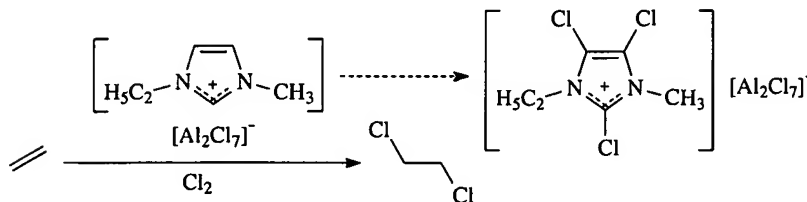
without the metals present [97]. Another metal-catalyzed nitration is the iron(III) nitrate-catalyzed nitration of phenol in dibutylimidazolium tetrafluoroborate [100]. Addition of dehydrating agents such as acetic anhydride or trifluoroacetic anhydride dramatically improved the reaction rate, but at the expense of producing the corresponding acetic or trifluoroacetic acid as a by-product [101].

The use of ultrasound has been shown to enhance the reaction rate in the nitration of phenols in  $[H_5C_2NH_3][NO_3]$  [102] with an  $Fe(NO_3)_3$  catalyst [103]. Significant improvements in selectivities and a ten-fold reduction in reaction time were observed compared with similar silent reactions.

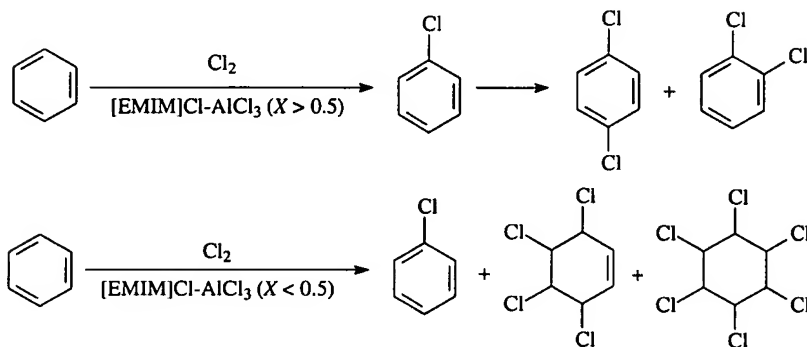
## 5.2.1.5 Electrophilic Halogenation Reactions

Another common reaction is the chlorination of alkenes to give 1,2-dihaloalkanes. Patell et al. have reported that the addition of chlorine to ethene in acidic chloroaluminate(III) ionic liquids gave 1,2-dichloroethane [104]. Under these conditions, the ring of imidazolium ionic liquid is chlorinated. Initially, the chlorination occurs at the 4- and 5- positions of the imidazole ring, and is followed by much slower chlorination at the 2-position. This does not affect the outcome of the alkene chlorination reaction and it was found that the chlorinated imidazolium ionic liquids are excellent catalysts for the reaction. This is shown in Scheme 5.2-45.

Wilkes and coworkers have investigated the chlorination of benzene in both acidic and basic chloroaluminate(III) ionic liquids [65]. In the acidic ionic liquid  $[EMIM]Cl-AlCl_3$  ( $X > 0.5$ ), the chlorination reaction initially gave chlorobenzene,



**Scheme 5.2-45** The chlorination of ethene to 1,2-dichloroethane [104].



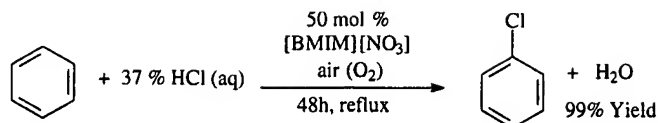
**Scheme 5.2-46** The chlorination of benzene in acidic and basic chloroaluminate ionic liquids [65].

which in turn reacts with a second molecule of chlorine to give dichlorobenzenes. In the basic ionic liquid, the reaction is more complex. In addition to the formation of chlorobenzene, addition products of chlorine and benzene are observed. These addition products include various isomers of tetrachlorocyclohexene and hexachlorocyclohexane (Scheme 5.2-46).

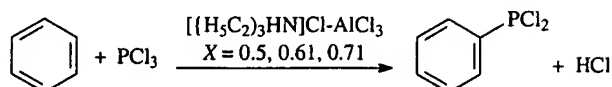
With a view to making halogenation reactions more atom efficient and reducing the amount of noxious waste products, an oxidative halogenation reaction was developed by Earle et al. [105]. Following the observation that the reaction of toluene with nitric acid in a halide ionic liquid gave halotoluenes as a mixture of isomers in quantitative yield, it was found that the reaction of hydrogen halide in a nitrate ionic liquid gave the same halotoluenes [97, 105]. The nitrate in this reaction was reduced to nitrogen monoxide (with the corresponding oxidation of halide to hypohalic acid), which in turn could be reoxidised spontaneously with air. The result is that ionic liquids such as [BMIM][NO<sub>3</sub>] catalyze the oxidative halogenation of arenes with hydrogen halides, using air as the oxidant (Scheme 5.2-47). The only by-product in this reaction is water, making this a very clean reaction [97].

The iodination of aromatic compounds using the electrophilic fluorinating agent 1-(chloromethyl)-1,4-diazabicyclo[2,2,2]octane tetrafluoroborate and iodine was carried out in a range of [BF<sub>4</sub>]<sup>-</sup> and [PF<sub>6</sub>]<sup>-</sup> ionic liquids and generally gave high yields [106]. Trihalide-based ionic liquids have been synthesised and the structure of the

## 318 | 5 Organic Synthesis



Scheme 5.2-47 The oxidative halogenation of benzene [97, 105].



Scheme 5.2-48 The phosphylation of benzene in acidic triethylammonium chloroaluminate(III) ionic liquids [112].

trihalide ions has been investigated by electrospray ionization mass spectroscopy and NMR. They are made by mixing equimolar amount of ICl with [HMIM][Cl] and IBr with [BMIM][Br] or alternatively Cl<sub>2</sub> or Br<sub>2</sub> with [EMIM][I]. These ionic liquids were used as reagent-solvents, or as reagents, by carrying out the reactions in [BMIM][PF<sub>6</sub>], in iodobromination and iodochlorination reactions of alkenes and alkynes. Furthermore, the addition of ICl and IBr to [BMIM][PF<sub>6</sub>] was investigated. Yields of *vic*-iodochloro or iodobromo adducts from very good to almost quantitative were observed for all the substrates examined [107]. The electrophilic addition of halogens to alkenes and alkynes was also investigated by Chiappe et al., in [BMIM][PF<sub>6</sub>] and [BMIM][BF<sub>4</sub>] [108, 109].

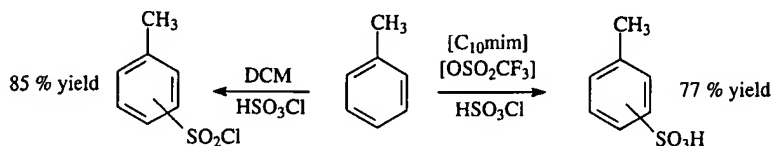
The bromination of aromatic compounds using *N*-bromosuccinimide (NBS) occurs in high yield in ionic liquids such as dibutylimidazolium tetrafluoroborate [110]. The yields of the monobrominated product were all in the 80% to 98% range. NBS was also used in the Wohl-Ziegler  $\alpha$ -bromination of aryl methyl groups [111]. The reaction in [BMIM][PF<sub>6</sub>] typically gave a 5 to 10% improvement in the yield, compared with a solvent-free reaction.

#### 5.2.1.6 Electrophilic Phosphylation Reactions

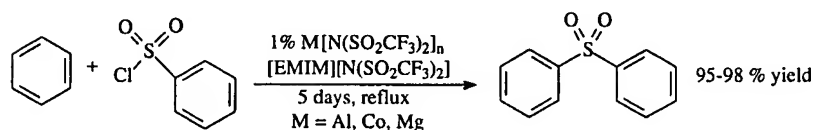
The Friedel-Crafts reaction of PCl<sub>3</sub> and benzene in [(C<sub>2</sub>H<sub>5</sub>)<sub>3</sub>HN]Cl-AlCl<sub>3</sub> ionic liquids was investigated for the synthesis of dichlorophenylphosphine [112]. A simple product isolation procedure was achieved as the product and ionic liquid formed separate phases at the end of the reaction. The effects of the ionic liquid composition, reactant composition, reaction time and quantity of ionic liquids on this reaction were studied (Scheme 5.2-48).

#### 5.2.1.7 Electrophilic Sulfonation Reactions

The sulfonation of aromatic compounds occurs readily in ionic liquids, with the simplest case being the direct sulfonation of aromatic compounds with sulfur trioxide to give the aryl sulfonic acid [113]. Ionic liquids such as triflate or triflimide ionic liquids were found to enhance the reaction rate. In the reaction of chlorosulfuric acid with aromatic compounds, the reaction in the ionic liquid gave a



**Scheme 5.2-49** The reaction of toluene with chlorosulfuric acid in ionic liquids and dichloromethane [113].



**Scheme 5.2-50** The benzenesulfonylation of benzene in an ionic liquid [47].

different product, compared with a similar reaction in dichloromethane. In the molecular solvent DCM the sulfonyl chloride was the major product, whereas in ionic liquid  $[\text{BMIM}][\text{OTf}]$  or  $[\text{C}_{10}\text{MIM}][\text{OTf}]$ , the sulfonic acid was the major product (Scheme 5.2-49) [113].

In chloroaluminate(III) ionic liquids such as  $[\text{BMIM}]\text{Cl}-\text{AlCl}_3$  ( $X = 0.50-0.67$ ) thionyl chloride forms diarylsulfoxides in 85–96% yield [114]. Sulfuryl chloride ( $\text{SO}_2\text{Cl}_2$ ) shows a different chemical reactivity in  $[\text{BMIM}][\text{N}(\text{SO}_2\text{CF}_3)_2]$ , where it halogenates the aromatic compound in quantitative yield [114]. By way of contrast, benzenesulfonyl chloride or methanesulfonyl chloride both sulfonylate aromatic compounds such as benzene or toluene in the presence of metal triflimide catalysts [47]. This is shown in Scheme 5.2-50. A similar reaction occurs in chloroaluminate(III) ionic liquids, but these suffer from the disadvantage that the separation of the product from the ionic liquid is difficult, without hydrolysing the ionic liquid [115].

## 5.2.2

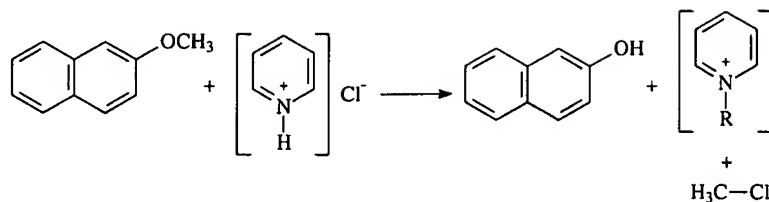
### Nucleophilic Reactions

#### 5.2.2.1 Aliphatic Nucleophilic Substitution Reactions

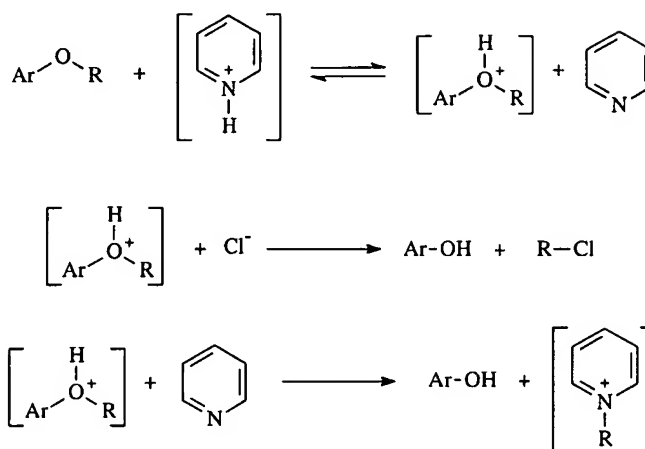
Nucleophilic substitution reactions involving molten salts are well known. A number of examples of molten pyridinium hydrochloride (mp  $144^\circ\text{C}$ ) being used in chemical synthesis, dating back to the 1940s, are known. Pyridinium chloride can act as both an acid and as a nucleophilic source of chloride. These properties are exploited in the dealkylation reactions of aromatic ethers [85]. An example involving the reaction of 2-methoxynaphthalene is given in Scheme 5.2-51 and a mechanistic explanation is given in Scheme 5.2-52.

Pyridinium chloride ( $[\text{PyH}]\text{Cl}$ ) has also been used in a number of cyclization reactions of aryl ethers [82, 85] (Scheme 5.2-53). Presumably the reaction initially

## 320 | 5 Organic Synthesis



8 **Scheme 5.2-51** The demethylation of 2-methoxynaphthalene to  
 9 2-naphthol with pyridinium chloride [16, 82].

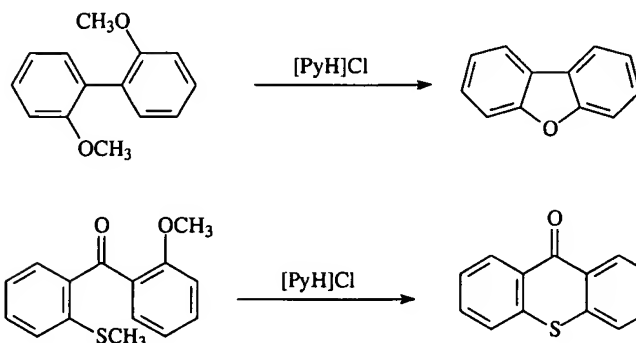


27 **Scheme 5.2-52** A mechanism for the dealkylation of aryl ethers with pyridinium chloride [116].

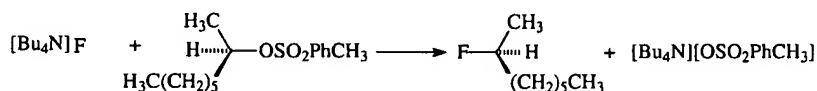
28  
 29  
 30 proceeds by dealkylation of the methyl ether groups to the corresponding phenol.  
 31 The mechanism of the cyclization is not well understood, but Pagni and Smith have  
 32 suggested that it proceeds via nucleophilic attack of an Ar-OH or Ar-O<sup>-</sup> group on  
 33 the second aromatic ring (in a protonated form) [85].

34 Tetrabutylammonium fluoride (TBAF) is usually used in the form of the trihy-  
 35 drate or as a solution in tetrahydrofuran (THF). The pure form is difficult to isolate,  
 36 owing to decomposition to HF, tributylamine and but-1-ene [82, 117] on dehydra-  
 37 tion. It has been used for a variety of reactions, including as a catalyst for various  
 38 reactions with silicon compounds [118, 119]. One of its main uses is in the cleavage  
 39 of silyl ether protecting groups [120]. TBAF has been used as a source of fluoride  
 40 ions in a number of substitution reactions studied by Cox et al. [121]. Alkyl and acyl  
 41 halides react with TBAF to give the corresponding alkyl or acyl fluoride in good yield.  
 42 In the reaction of (*R*)-2-tosyloctane with TBAF, the product was (*S*)-2-fluorooctane,  
 43 confirming an S<sub>N</sub>2 type mechanism in the substitution reaction (Scheme 5.2-54).

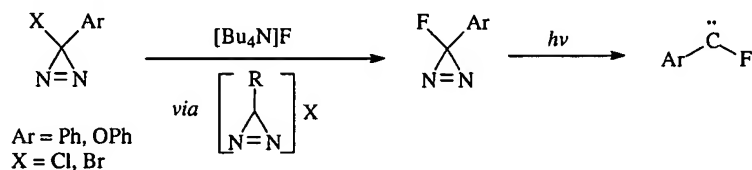
44 TBAF has also been used in the preparation of various fluorocarbenes. This  
 45 involved the photolysis of phenyl- or phenoxyfluorodiazirine, which was in turn



Scheme 5.2-53 Two examples of aryl demethylation reactions followed by cyclization [82, 85].



Scheme 5.2-54 The use of TBAF in an  $S_N2$  substitution reaction [82, 121].



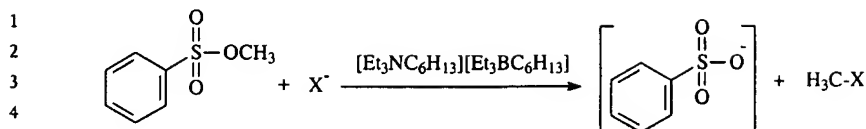
Scheme 5.2-55 The use of TBAF in the preparation of a fluorodiazirine [122, 123].

synthesized from the reaction of TBAF with phenyl- or phenoxyhalodiazirine as in Scheme 5.2-55 [122, 123].

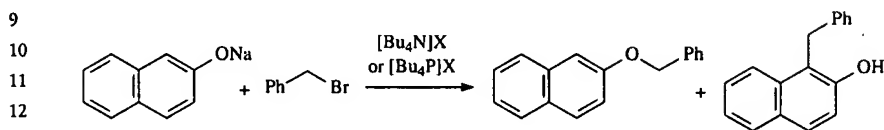
The first attempt at a nucleophilic substitution reaction in an ionic liquid was carried out by Ford and coworkers [124–126]. Here, the rates of reaction of halide ion (in the form of its triethylammonium salt) with methyl tosylate in the molten salt triethylhexylammonium triethylhexylborate were studied (Scheme 5.2-56). This was compared with similar reactions in dimethyl formamide (DMF) and methanol. The reaction rates in the molten salt appeared to be intermediate in rate between methanol and DMF (a dipolar aprotic solvent known to accelerate  $S_N2$  substitution reactions).

The alkylation of sodium 2-naphthoxide with benzyl bromide in tetrabutylammonium and tetrabutylphosphonium halide salts was investigated by Brunet and Badri [127] (Scheme 5.2-57). The yields in this reaction were quantitative and alkylation occurred predominantly on the oxygen atom of the naphthoxide ion (typically 93–97%). The rate of the reaction was slower in the chloride salts due to the benzyl bromide reacting with chloride ion to give the less reactive benzyl chloride.

## 322 | 5 Organic Synthesis



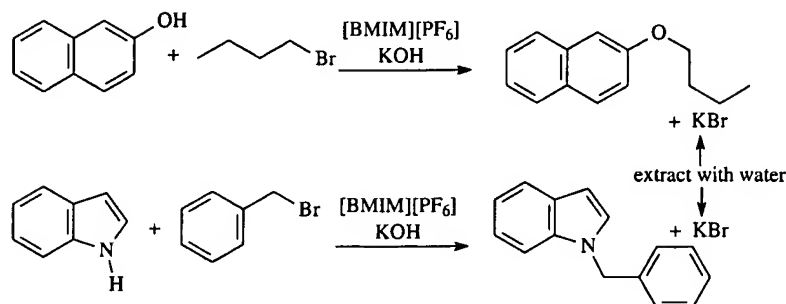
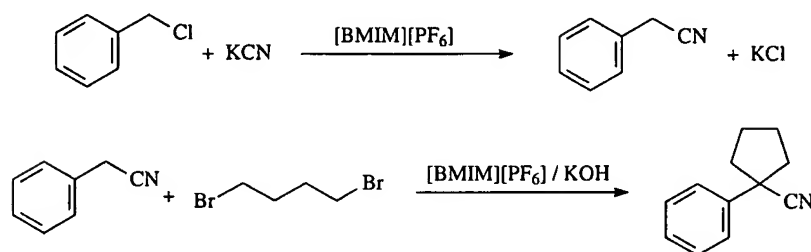
6 **Scheme 5.2-56** The reaction of halide with methyl tosylate in  
7 triethylhexylammonium triethylhexylborate [124–126].



14 **Scheme 5.2-57** The benzylation of sodium 2-naphthoxide with benzyl  
15 bromide in ammonium or phosphonium halide salts (X = Cl, Br) [127].

16  
17  
18 Indole and 2-naphthol undergo alkylation on the nitrogen and oxygen atoms  
19 respectively (Scheme 5.2-58), when treated with an alkyl halide and base (usually  
20 NaOH or KOH) in [BMIM][PF<sub>6</sub>] [128]. These reactions occur with similar rates to  
21 those carried out in dipolar aprotic solvents such as DMF or DMSO. An advantage  
22 of using the room-temperature ionic liquid for this reaction is that the lower re-  
23 action temperatures result in higher selectivities for substitution on the oxygen or  
24 nitrogen atoms. The by-product (sodium or potassium halide) of the reaction can  
25 be extracted with water and the ionic liquid recycled. Indole was also benzylated by  
26 reaction with dibenzyl carbonate (DBC) using DABCO as a catalyst in 80% yield in  
27 tetrabutylammonium chloride [129]. Similarly, a wide range of halide, [BF<sub>4</sub>]<sup>−</sup> and  
28 [PF<sub>6</sub>]<sup>−</sup> ionic liquids were used in the alkylation of benzimidazole in with DBC in  
29 74 to 95% yield [129]. The ionic liquid reactions all gave higher yields when the  
30 ionic liquid was present, compared with a similar reaction in acetonitrile. Potas-  
31 sium fluoride has been used as a promoter for the benzylation of phthalimide with  
32 benzyl chloride in imidazolium and pyridinium ionic liquids in 91 to 97% yields  
33 [130]. Benzyl cinnamate formation from potassium cinnamate and benzyl chloride  
34 proceeds considerably faster in ionic liquids than in the dipolar aprotic solvent  
35 DMF. The ionic liquid [BMIM][BF<sub>4</sub>] showed the greatest catalytic capability (97%  
36 yield) and the ionic liquid could be recycled and reused [131]. A quantitative study  
37 of the nucleophilic displacement reaction of benzoyl chloride with cyanide ion in  
38 [BMIM][PF<sub>6</sub>] was investigated by Eckert and coworkers [132]. The separation of  
39 the product 1-phenylacetonitrile from the ionic liquid was achieved by distillation  
40 or by extraction with supercritical CO<sub>2</sub>. 1-Phenylacetonitrile was then treated with  
41 KOH in [BMIM][PF<sub>6</sub>] to generate an anion, which reacted with 1,4-dibromobutane  
42 to give 1-cyano-1-phenylcyclopentane (Scheme 5.2-59). This was in turn extracted  
43 from the ionic liquid with supercritical CO<sub>2</sub>. These reactions lead to a build up of  
44 KCl or KBr in the ionic liquid, which was removed by washing the ionic liquid with  
45 water.

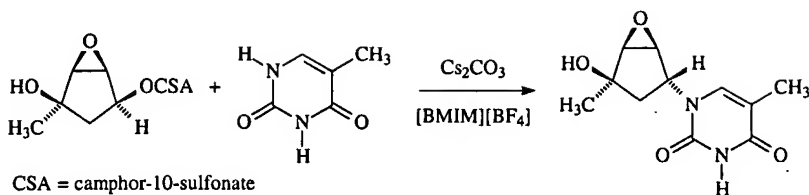


Scheme 5.2-58 Alkylation reactions in [BMIM][PF<sub>6</sub>] [128].

Scheme 5.2-59 The reaction of cyanide with benzyl chloride and its subsequent reaction with 1,4-dibromobutane [132].

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Nucleophilic displacement reactions have been carried out under aqueous biphasic conditions with water and the immiscible ionic liquid [BMIM][PF<sub>6</sub>]. Nucleophiles such as azide, cyanide, phenoxide and 4-chlorophenoxide all demonstrated good yields in the reaction with a range of alkyl bromides [133]. The addition of a chiral phase transfer catalyst did not result in any observed stereoselectivity. [BMIM][PF<sub>6</sub>] and [BMIM][BF<sub>4</sub>] have also been used as solvents in the alkylation of benzotriazole [134] and sodium benzenesulfonates [135]. A range of aromatic alkyl ethers were synthesized in [BMIM][PF<sub>6</sub>], [BF<sub>4</sub>], [OTf], [SbF<sub>6</sub>] and [O<sub>2</sub>CCH<sub>3</sub>] by Chi et al., by the reaction of an alcohol with an alkyl bromide. This was without a base present and therefore required higher reaction temperatures (100 °C) [136]. Chi also reports nucleophilic displacement of alkylmethane sulfonates with halides, cyanide and alkoxides [137]. This methodology has been applied with <sup>18</sup>F labeling of molecules [138]. Headley et al. have reported similar substitution reactions of a more functionalized alkyl halide [139]. An example of nucleophilic substitution has been used in the formation of constrained carbanucleosides. This shows that the reaction proceeds through a classic S<sub>N</sub>2 mechanism, since the stereochemistry at the nucleophilic site has been inverted [140]. The reactions in [BMIM][BF<sub>4</sub>] gave typical improvements in yield from 15% to 70%. This is shown in Scheme 5.2-60.



**Scheme 5.2-60** The formation of carbanucleosides in [BMIM][BF<sub>4</sub>] [140].

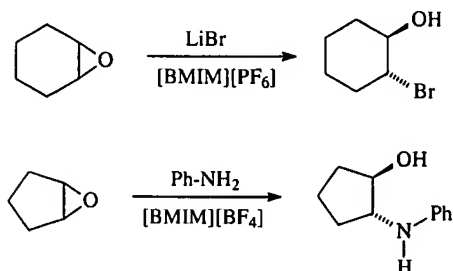
Welton and coworkers have published a series of papers seeking to understand the kinetics and how the structure of ionic liquids affects nucleophilic substitution reactions. The reactions of imidazolium halides with methyl 4-nitrosylate in [BMIM][BF<sub>4</sub>] were examined using UV-visible spectrophotometry [141]. The effect of the structure of the cation on the reaction rate in triflimide ionic liquids [142] and the effect of changing the anion in [BMIM]<sup>+</sup> ionic liquids are described [143]. Welton finds that the rates of reactions where the starting materials are charge neutral and the formation of the activated complex involves the development of charges will be accelerated by the use of an ionic liquid solvent. This is an extension of the Hughes–Ingold rule (devised for molecular solvents) to ionic liquids, showing them to be highly polar solvents. Where the formation of hydrogen bonds between a nucleophile and the anion of an ionic liquid is possible, the reaction will be further accelerated [144].

The conversion of alcohols to halides has been described by several authors. Nguyen et al. have used imidazolium halide ionic liquids in the conversion of fatty alcohols to fatty alkyl halides with sodium bromide or sodium iodide [145]. This procedure can be used with direct or microwave heating. Tang describes a similar reaction (the halogenation of diols) using hydrohalic acid and has the advantage that water is the only byproduct [146]. The halogenation of diols is also described by Nguyen [147].

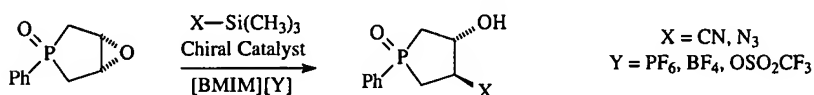
[BMIM][PF<sub>6</sub>] has been used as a solvent for the nucleophilic addition of lithium halide to epoxides to give a vicinal halohydrin [148]. This nucleophilic addition was also found to work well with amines in [BMIM][BF<sub>4</sub>] to give β-amino alcohols [149]. These two reactions are shown in Scheme 5.2-61.

A similar reaction is the use of TMS azide and TMS cyanide in the ring opening of epoxides (Scheme 5.2-62) [150]. The authors use chiral catalysts such as Salen-Al or Ti(O<sup>i</sup>Pr)<sub>4</sub>/TADDOL, which give the expected addition product and with a modest enantioselectivity. Khodaei et al. have carried out nucleophilic addition and ring opening of epoxides with aromatic amines in the salt tetrabutylammonium bromide, with several bismuth catalysts [151]. These reactions gave excellent yields and improved reaction rates over conventional solvents.

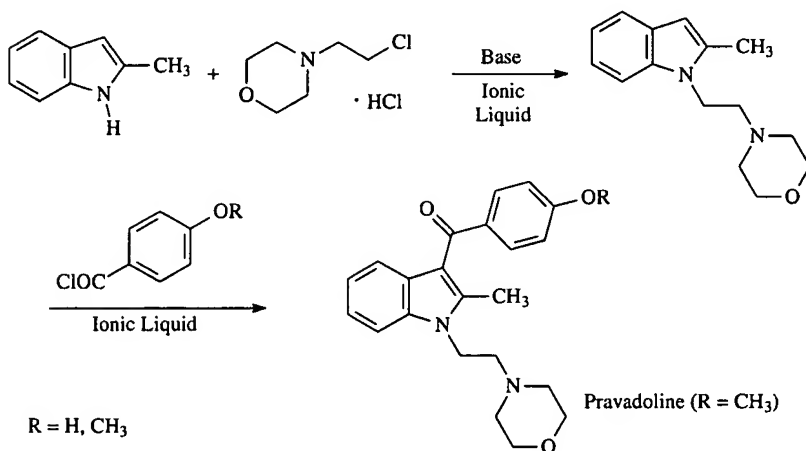
As a demonstration of the complete synthesis of a pharmaceutical in an ionic liquid, Pravadolone was selected as it combines a Friedel–Crafts reaction and a nucleophilic displacement reaction (Scheme 5.2-63) [152]. The alkylation of 2-methylindole with 1-(*N*-morpholino)-2-chloroethane occurs readily in [BMIM][PF<sub>6</sub>]



**Scheme 5.2-61** The nucleophilic ring opening of epoxides with halides and amines [148, 149].



**Scheme 5.2-62** The addition of TMS-CN or TMS-N<sub>3</sub> to epoxides in ionic liquids [150].

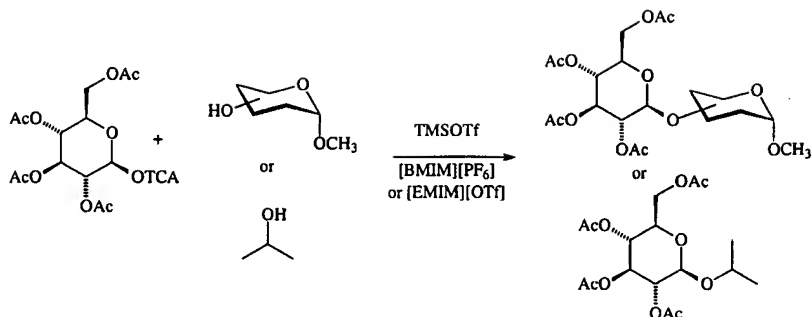


**Scheme 5.2-63** The complete synthesis of Pravadoline in [BMIM][PF<sub>6</sub>] [152].

and [BMMIM][PF<sub>6</sub>] (BMMIM = 1-butyl-2,3-dimethylimidazolium), in 95–99% yields, respectively, using potassium hydroxide as the base. The Friedel-Crafts acylation step in [BMIM][PF<sub>6</sub>] at 150 °C occurs in 95% yield and requires no catalyst.

The substitution of trichloroacetimidates with alcohols and glycosides was attempted in [BMIM][PF<sub>6</sub>] and [EMIM][OTf] [153]. The reactions proceeded to give the appropriate isopropyl or glucoside substitution product in moderate to good yields. These and similar glycosidation reactions are also described by Pakulski [154]. An example is shown in Scheme 5.2-64.

## 326 | 5 Organic Synthesis



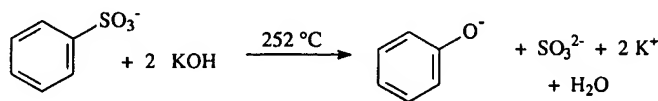
**Scheme 5.2-64** The TMSOTf catalyzed substitution of trichloroacetimidate in ionic liquids [154].

Shreeve et al. have synthesized a range of new ionic liquids based on oxazolidine, morpholine and 1,2,4-triazole. These have been found to be good solvents for the Cu(I)-mediated nucleophilic trifluoromethylation of benzyl bromide [155]. Nucleophilic substitution has also been carried out on alkenes in the form of 2-tosyltropone, where the tosyl group was substituted for a chloride in [BMIM][BF<sub>4</sub>] [156]. Aminopyridines [157] and aminopyrimidines [158] react with  $\alpha$ -halo ketones to form imidazopyridines and imidazopyrimidines. These reactions have been investigated in [BF<sub>4</sub>] and [PF<sub>6</sub>] ionic liquids and found to give faster reaction rates than in organic solvents [159].

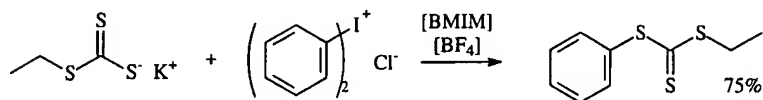
#### 5.2.2.2 Aromatic Nucleophilic Substitution Reactions

Molten salts have been used for many years in the form of reagents such as fused KOH, pyridinium chloride and tetrabutylammonium fluoride (TBAF) [160]. One of the earliest examples of a molten salt in the literature involves the use of KOH. Examples, dating from 1840 [161] are known. A common use is in the reaction of fused KOH with arene sulfonic acids to produce phenols. Although KOH has a high melting point (410 °C), impurities such as traces of water or carbonates bring the melting point down. An example is given in Scheme 5.2-65 [162].

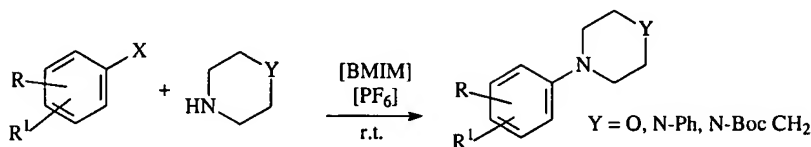
Diaryliodonium salts undergo a nucleophilic displacement reaction in [BMIM][BF<sub>4</sub>] with potassium trithiocarbonates to give aryltrithiocarbonates (Scheme 5.2-66) [163]. The reactions in ionic liquids gave significantly higher yields (up to 75%) than in solvents such as THF, DMF, or acetonitrile. Diaryliodonium



**Scheme 5.2-65** The reaction of benzenesulfonates with fused KOH [161, 162].



Scheme 5.2-66 The preparation of aryltrithiocarbonates.



Scheme 5.2-67 The amination of aryl halides in  $[\text{BMIM}][\text{PF}_6]$  [165].

salts have also been used to arylate indoles and benzimidazoles in  $[\text{BMIM}][\text{BF}_4]$  [164].

The amination of aryl halides has been carried out in  $[\text{BMIM}][\text{BF}_4]$  and  $[\text{BMIM}][\text{PF}_6]$  by Yadav and coworkers [165]. Conventionally, these reactions are carried out in dipolar aprotic solvents such as DMF or DMSO, and require high reaction temperatures. However, in  $[\text{BMIM}][\text{PF}_6]$ , these reactions have been shown to proceed at room temperature (Scheme 5.2-67).

A related reaction is the substitution of sulfonate leaving groups with halide ion in 2-substituted tropones [156]. In these reactions, lithium ion is thought by the authors to catalyze the reaction.

### 5.2.3

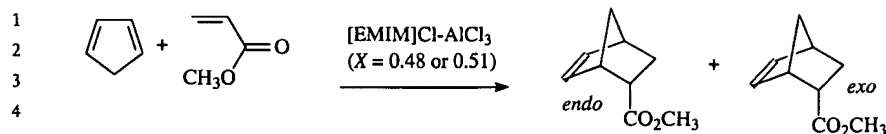
#### Electrocyclic Reactions

##### 5.2.3.1 Diels-Alder Reactions

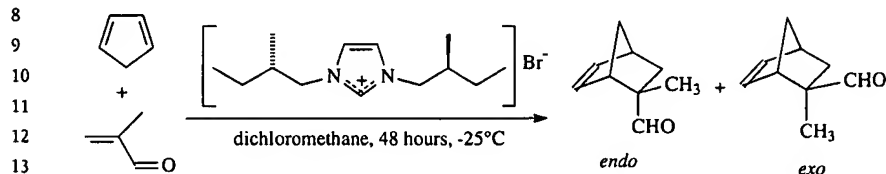
Lee has used chloroaluminate(III) ionic liquids in the Diels-Alder reaction [166]. The *endo:exo* ratio rose from 5.25 to 19 by changing the composition of the ionic liquid from  $X = 0.48$  to  $X = 0.51$  (Scheme 5.2-68). The reaction works well giving up to 95% yield, but the moisture sensitivity of these systems is a major disadvantage and the products were recovered by quenching the ionic liquid in water. A by-product of the reactions involving cyclopentadiene is the formation of its dimer, and this dimerization reaction in acidic chloroaluminate(III) ionic liquids was investigated [167]. Unsurprisingly, it was found that the rate of dimerization was a function of the acidity of the ionic liquid. Kumar has also investigated a means of converting an *exo*-selective Diels-Alder reaction to an *endo*-selective reaction, by means of altering the acidity of chloroaluminate(III) ionic liquids [168]. Generally the yields in most of these chemical reactions are too low to be useful, and suffer the usual product isolation problems of chloroaluminate(III) ionic liquids.

Neutral ionic liquids have been found to be excellent solvents for the Diels-Alder reaction. The first example of a Diels-Alder reaction in an ionic liquid was in the

## 328 | 5 Organic Synthesis



Scheme 5.2-68 The Diels-Alder reaction in a chloroaluminate(III) ionic liquid [166].



Scheme 5.2-69 Use of a chiral ionic liquid in a Diels-Alder reaction [170].

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reaction of methyl acrylate with cyclopentadiene in [EtNH<sub>3</sub>][NO<sub>3</sub>] [169], where significant rate enhancement was observed. Howarth et al. investigated the role of chiral imidazolium chloride and trifluoroacetate salts (dissolved in dichloromethane) in the Diels-Alder reaction of cyclopentadiene and either crotonaldehyde or methacrolin [170]. It should be noted that this paper describes one of the first examples of a chiral cationic ionic liquid being used in synthesis (Scheme 5.2-69). The enantioselectivity was found to be <5% in this reaction for both the *endo* (10%) and *exo* (90%) isomers.

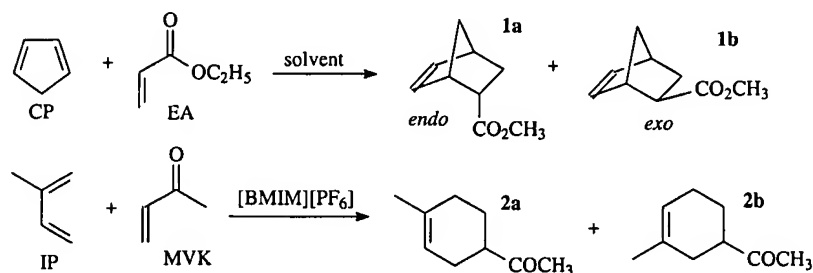
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A study of the Diels-Alder reaction was carried out by Earle et al. [171]. The rates and selectivities of reactions of ethyl acrylate (EA) with cyclopentadiene (CP) in water, 5 M lithium perchlorate in diethyl ether (5 M LPDE), and [BMIM][PF<sub>6</sub>] were compared. The reactions in the ionic liquid [BMIM][PF<sub>6</sub>] are marginally faster than in water, but are both slower than in 5 M LPDE [43, 172] (see Table 5.2-3 and Scheme 5.2-18). It should be noted that these three reactions give up to 98% yield if left for 24 h. The *endo:exo* selectivity in [BMIM][PF<sub>6</sub>] was similar to 5 M LPDE, and considerably greater than that in water (Table 5.2-4).

Table 5.2-4 Diels-Alder reactions in various solvents [165].

Solvent	Diene	Dieneophile	Product	Time	Yield	a:b ratio
[BMIM][PF <sub>6</sub> ]	CP	EA	1a + 1b	1	36	8.0
5M LPDE	CP	EA	1a + 1b	1	61	8.0
Water	CP	EA	1a + 1b	1	30	3.5
[BMIM][PF <sub>6</sub> ] <sup>a</sup>	IP	MVK	2a + 2b	6	98	20
[BMIM][PF <sub>6</sub> ]	IP	MVK	2a + 2b	18	11	4

<sup>a</sup>5 mol% ZnI<sub>2</sub> added, IP = isoprene.



Scheme 5.2-70 The Diels-Alder reactions in Table 5.2-4 [171].

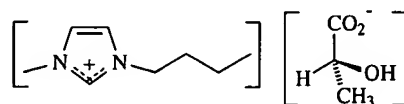
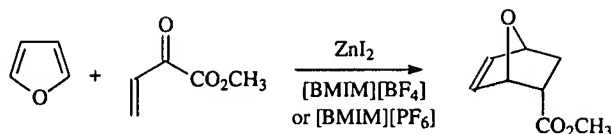


Fig. 5.2-4 An example of a chiral ionic liquid used in the Diels-Alder reaction [43].

In the reaction of isoprene (IP) with methyl vinyl ketone (MVK), the selectivities of the two isomers produced in this reaction can be improved from 4:1 to 20:1 by the addition of a mild Lewis acid such as zinc(II) iodide (5 mol%) to the ionic liquid [BMIM][PF<sub>6</sub>] (Scheme 5.2-70). One of the key benefits of this is that the ionic liquid and catalyst can be recycled and reused after solvent extraction or direct distillation of the product from the ionic liquid. The reaction was also carried out in the chiral ionic liquid [BMIM][lactate] (Fig. 5.2-4). This was found to give the fastest reaction rates of all the ionic liquids tested, and the lowest *endo:exo* selectivity. The products of the Diels-Alder reaction were found to be racemic and no chiral induction was observed [171].

A similar study was performed by Welton and coworkers, who studied the rate and selectivities of the Diels-Alder reaction of cyclopentadiene with methyl acrylate in a number of neutral ionic liquids [173]. It was found that *endo:exo* ratios decreased slightly as the reaction proceeded, and were dependent on reagent concentration and ionic liquid type. A further study showed that the degree of hydrogen bonding to the ionic liquid of solvent affected the *endo:exo* ratio, with greater hydrogen bonding giving greater *endo*-selectivity [174].

The use of molten salts based on phosphonium tosylates has also been reported for Diels-Alder reactions [175]. These salts have higher melting points than most ionic liquids in common use and hence the reactions were performed in a sealed tube. The authors claim very high selectivities in the reaction of isoprene with MVK or methyl acrylate. The effect of temperature on the selectivity in phosphonium tosylates gave reduced *endo:exo* ratios at higher temperatures [176]. The Diels-Alder reactions of isoprene with acrylonitrile, acrylic acid and methacrylic acid in pyridinium ionic liquids ([EtPy][BF<sub>4</sub>] or [EtPy][F<sub>3</sub>CCO<sub>2</sub>]) were found to give the expected cyclohexene structures [177]. The authors show that



**Scheme 5.2-71** The Diels-Alder reaction of furan catalyzed by zinc(II) iodide [180].

far better yields and selectivities are obtained, when compared with a molecular solvent (dichloromethane), and that these ionic liquids give improved performance over phosphonium tosylates. Another class of ionic liquids used in this reaction are binary zinc(II) halide-containing salts. These mildly Lewis acidic binary ionic liquids gave enhanced selectivities over neutral ionic liquids (12:1 *endo:exo* ratio compared with typically 5:1) [178]. Choline chloride–zinc chloride binary ionic liquids have also been used for these reactions [179]. The Diels-Alder reaction can also be carried out successfully on furan, thiophene and pyrroles in [BMIM][BF<sub>4</sub>] or [BMIM][PF<sub>6</sub>] [180]. This is shown in Scheme 5.2-71. Another example of the use of metal salts to enhance the Diels-Alder reaction in ionic liquids is in the addition of small amounts of scandium(III) triflate to [BMIM][OTf] [181]. The reaction in the ionic liquid gave over 10 times the reaction rate (1,4-naphthaquinone + 2,3-dimethylbutadiene) compared to a similar reaction in dichloromethane.

Oh and Meracz looked at the use of chiral auxiliaries to control the stereochemical outcome of the Diels-Alder reaction [182]. The reactions in some cases gave very good enantioselectivities, and complete *endo*-selectivity. The authors also investigated the use of a chiral bis-oxazoline copper(II) complex, which also gave high enantioselectivities (96:4 ratio). These two reactions are shown in Scheme 5.2-72. Another asymmetric Diels-Alder reaction (Scheme 5.2-73) used a chiral platinum(II) complex, and gave 90–93% *ee* in the reaction of cyclopentadiene with an oxazolinoyl  $\alpha,\beta$ -unsaturated ketone [183]. When the reaction was carried out in a molecular solvent such as dichloromethane, the platinum catalyst underwent racemisation, and hence significantly reduced the *ee* of the product. In the ionic liquids investigated, racemization did not occur. Hence the ionic liquids were acting to stabilise the catalyst.

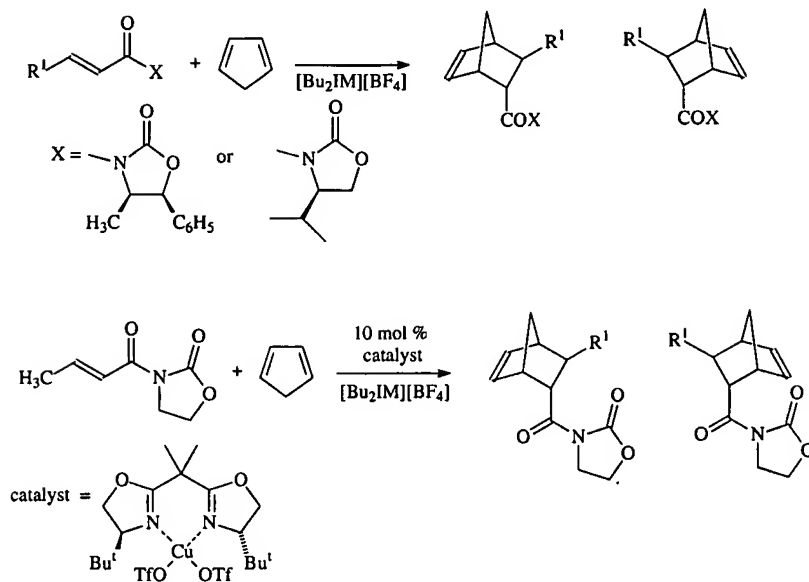
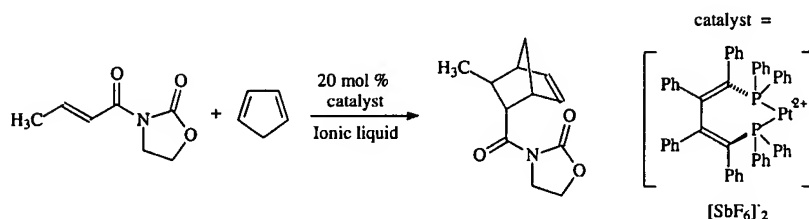
### 5.2.3.2 Hetero Diels-Alder Reactions

Kitazume and Zulfiqar have investigated the *aza*-Diels-Alder reaction in 1,8-diazabicyclo[5.4.0]-7-undecenium trifluoromethanesulfonate [EtDBU][OTf] [184] (Fig. 5.2-5). This reaction involved the scandium(III) trifluoromethanesulfonate catalyzed reaction of an imine (usually generated *in situ* from an aldehyde and an amine) with a diene. An example of this reaction is given in Scheme 5.2-74. The yields in this reaction were high (80–99%) and it was found that the ionic liquid could be recycled and reused.

Yadav has demonstrated another *aza*-Diels-Alder reaction in the formation of pyrano- and furanoquinolines from anilines, aldehydes and dihydropyran or dihydrofuran in ionic liquids such as [BMIM][BF<sub>4</sub>] [185]. The reaction involves the



## 5.2 Stoichiometric Organic Reactions and Acid-catalyzed Reactions in Ionic Liquids 331

Scheme 5.2-72 The asymmetric Diels-Alder reaction in [Bu<sub>2</sub>IM][BF<sub>4</sub>] [182].

Scheme 5.2-73 The Pt-NUPHOS catalyzed asymmetric Diels-Alder reaction [183].

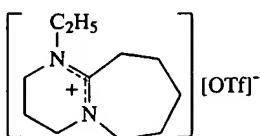
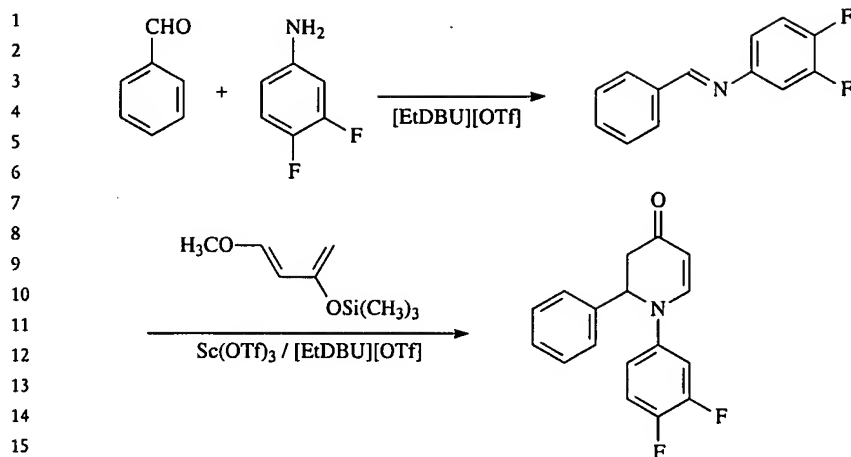


Fig. 5.2-5 The structure of diazabicyclo[5.4.0]-7-undecenium trifluoro methanesulfonate [EtDBU][OTf] [184].

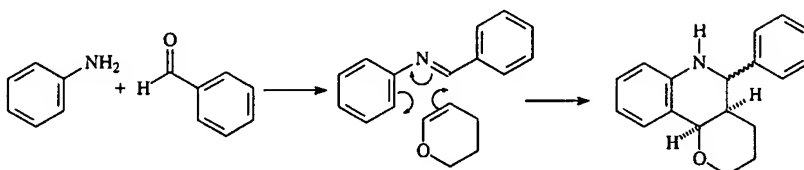
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condensation of the aromatic amine with the aldehyde to give an aromatic imine followed by a Diels-Alder reaction, to give the cyclized product in up to 92% yield. An example is shown in Scheme 5.2-75. Yadav also describes a more elaborate hetero Diels-Alder reaction, shown in Scheme 5.2-76. Here the aldehyde undergoes a condensation reaction with the  $\beta$ -dicarbonyl compound followed by a hetero-Diels-Alder reaction in [BMIM][BF<sub>4</sub>] [186].

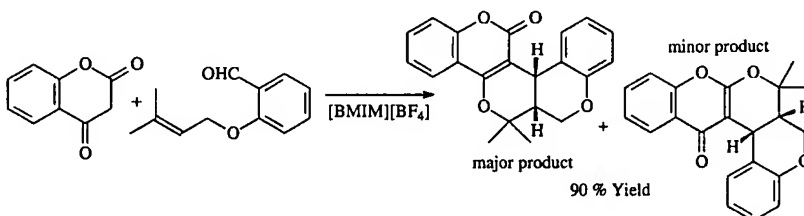
## 332 | 5 Organic Synthesis



Scheme 5.2-74 The aza-Diels-Alder reaction in an ionic liquid [169].



Scheme 5.2-75 The aza-Diels-Alder reaction in ionic liquids [185].



Scheme 5.2-76 The Knoevenagel hetero-Diels-Alder reaction coumarin synthesis [186].

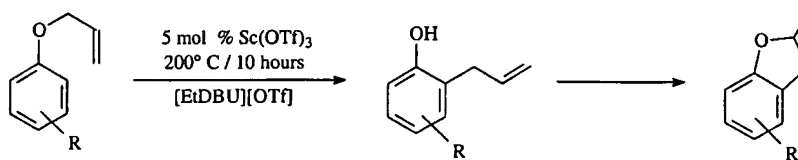
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Microwave irradiation has been used to dramatically reduce reaction times in a number of hetero Diels-Alder reactions [187], using  $[\text{BMIM}][\text{PF}_6]$  dissolved in dichloroethane to promote the absorption of microwave energy.

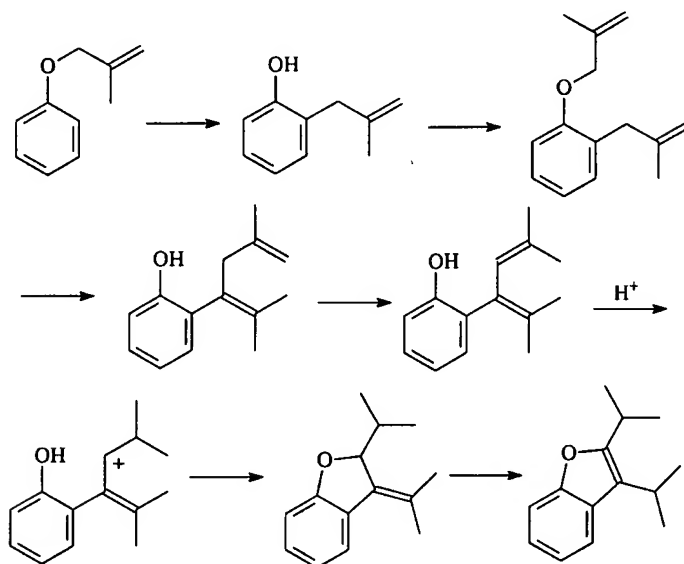
## 5.2.3.3 The Ene Reaction

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Kitazume and Zulfiqar have investigated the Claisen rearrangement of several aromatic allyl ethers in ionic liquids, catalyzed by scandium(III) trifluoromethanesulfonate [188]. The reaction initially gave the 2-allylphenol but this reacted further to



**Scheme 5.2-77** The Claisen rearrangement of several phenyl allyl ethers ( $\text{R} = \text{H}$ , 4- $\text{CH}_3$ , 6- $\text{CH}_3$ ) [188].

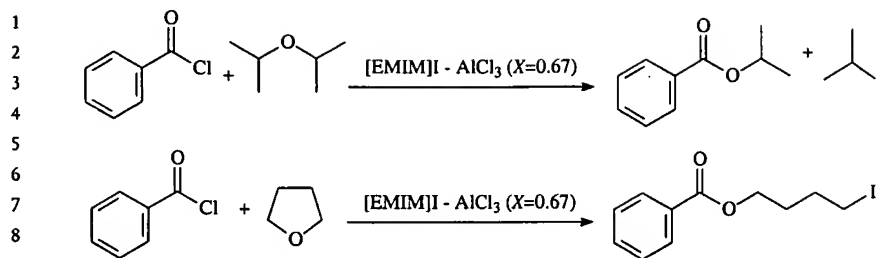


**Scheme 5.2-78** Proposed mechanism for the formation of 2,3-diisopropylbenzo[b]furan [188].

give 2-methyl-2,3-dihydrobenzo[b]furan (Scheme 5.2-77). The yields in this reaction were highly dependent on the ionic liquid chosen, with  $[\text{EtDBU}][\text{OTf}]$  giving the best yields (e.g. 91% for  $\text{R} = 6\text{-CH}_3$ ). Reactions in  $[\text{BMIM}][\text{BF}_4]$  and  $[\text{BMIM}][\text{PF}_6]$  gave low yields (9–12%).

In order to confirm that 2-allylphenol was indeed an intermediate in the reaction, the authors subjected 2-allylphenol to the same reaction conditions and found that it rearranged to give 2-methyl-2,3-dihydrobenzo[b]furan. In the reaction of 2-methyl-2-propenyl phenyl ether under similar conditions, 2,3-diisopropylbenzo[b]furan was isolated in 15% yield. A plausible mechanistic scheme is given by the authors (Scheme 5.2-78). It involves the Claisen rearrangement of 2-methyl-2-propenyl phenyl ether to 2-(2-methyl-2-propenyl)phenol, followed by a transalkylation of a 2-methylpropenyl group to the phenyl OH group. This undergoes further rearrangements and cyclization to give the 2,3-diisopropylbenzo[b]furan [188].

## 334 | 5 Organic Synthesis



Scheme 5.2-79 The acylative cleavage of ethers in an ionic liquid [190].

## 5.2.4

## Addition Reactions (to C=C and C=O Double Bonds)

## 5.2.4.1 Esterification Reactions (Addition to C=O)

Esterification reactions readily occur in ionic liquids. A simple example is the reaction of acetic, decanoic and octadecanoic acid with alcohols such as methanol, 1-butanol or 1-octanol. Here, Tang et al. used the ionic liquid  $[H-MIM][BF_4]$  (this is a simple mixture of 1-methylimidazole and tetrafluoroboric acid) as a solvent and catalyst for the reaction [189]. Singer and coworkers have shown that benzoyl chloride reacts with ethers to give alkyl benzoates [190] in chloroaluminate(III) ionic liquids. This reaction results in the acylative cleavage of ethers, and a number of reactions with cyclic and acyclic ethers were investigated in the ionic liquid  $[EMIM]I-AlCl_3$  ( $X = 0.67$ ). Two examples are shown in Scheme 5.2-79.

Esterification reactions can be catalyzed by the ionic liquid 1-butylpyridinium chloride ( $[BPY]Cl-AlCl_3$  ( $X = 0.33$ )) [191, 192]. Deng and coworkers found that higher yields were obtained compared to similar reactions with a sulfuric acid catalyst. A number of primary, secondary and tertiary alcohols were acylated with acetic acid and acetic anhydride in  $[BMIM][PF_6]$  using metal catalysts [193]. These reactions work well initially, but the catalyst becomes ineffective when the ionic liquid/catalyst is recycled. The authors do not give an explanation for this, however it is known that the  $[PF_6]^-$  ion dissociates to phosphate and fluoride ions under aqueous conditions and this could lead to catalyst being turned into an inactive fluoride salt [194]. Two examples of the use of Brønsted acidic ionic liquids, where the acid group is in the cation and their use in esterification reactions were published a year later. The first uses 3-(triphenylphosphonium)propanesulfonic acid[tosylate] (Fig. 5.2-6) in the formation of ethyl acetate [195] and the second uses 1-(3-methylimidazolium)butanesulfonic acid[trifluoromethanesulfonate] (Fig. 5.2-6) in the esterification of acetic acid with alkenes [196].

Ultrasound has been used in the acetylation of a range of alcohols in dibutylimidazolium bromide [197]. Generally a 5 to 10 times enhancement in the reaction rate is observed when compared with the equivalent silent reaction. 1,3-dialkylimidazolium benzoate ionic liquids have been used in the benzylation of glucose with benzoic anhydride (Scheme 5.2-80) [198]. The reaction was found to

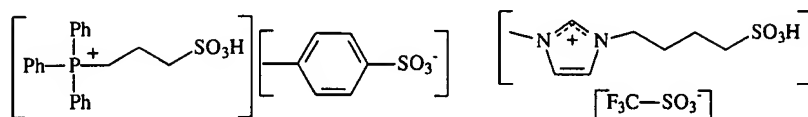
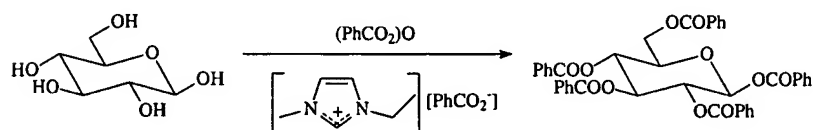


Fig. 5.2-6 Brønsted acidic ionic liquids used in esterification reactions [195, 196].

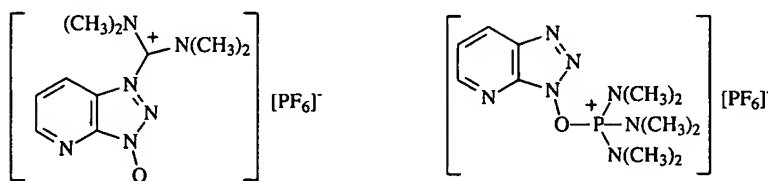
Scheme 5.2-80 Peracylation of  $\beta$ -D-glucose in 1-ethyl-3-methylimidazolium benzoate [198].

work well with anhydrides, but failed when acid chlorides were employed. The authors state that the basicity of the benzoate ion is responsible for promoting the reaction. A similar reaction was described by MacFarlane et al. [199]. Here [BMIM][N(CN)<sub>2</sub>] was used to promote the acetylation of glucose with acetic anhydride. The dicyanamide ion is mildly basic and was shown to act as a catalyst.

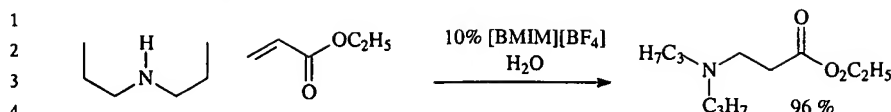
A popular way to form esters and amides is to use a coupling reagent such as dicyclohexylcarbodiimide (DCC). This has been used to form phenolic esters of ferrocenemonocarboxylic acid in [BMIM][BF<sub>4</sub>] and [BMIM][PF<sub>6</sub>] in high yield [200]. Unfortunately, the by-product dicyclohexyl urea builds up in the ionic liquid and the authors do not explain how it can be removed from the ionic liquids chosen.

#### 5.2.4.2 Amide Formation Reactions (Addition to C=O)

The first example of a peptide synthesis in an ionic liquid was described by Plaquevent et al. [BMIM][PF<sub>6</sub>] was used as a solvent for natural and synthetic amino acids, which were coupled with two ionic coupling agents based on triazoles [201] (Fig. 5.2-7). If no coupling agent or DCC was used, no reaction was observed. Yields as high as 87% were observed and the type of extraction procedure used made a significant difference to the isolated yields.

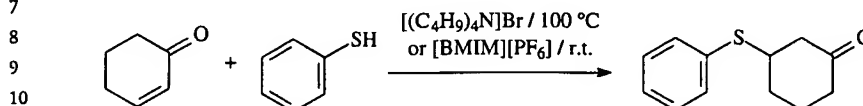
Fig. 5.2-7 The structure of two ionic [PF<sub>6</sub>] peptide coupling agents [201].

## 336 | 5 Organic Synthesis



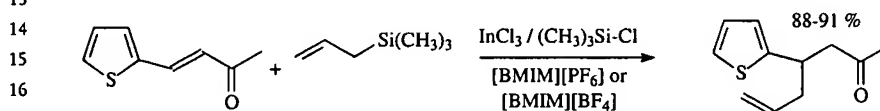
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**Scheme 5.2-81** The Michael addition of dipropylamine to ethyl acrylate [202].



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**Scheme 5.2-82** The addition of thiols to cyclohexeneone [205, 206].



**Scheme 5.2-83** The Sakurai reaction in ionic liquids [207].

#### 5.2.4.3 The Michael Reaction (Addition to C=C)

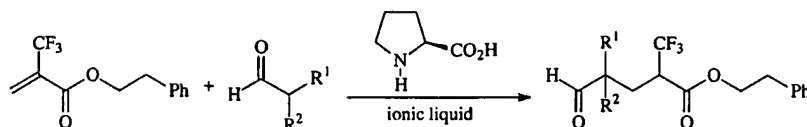
The Michael reaction proceeds very efficiently in many ionic liquids. Traditionally, metal catalysts are used to promote the reaction, however, these catalysts are not necessary in ionic liquids. Xia et al. have found that amines reacts with ethyl or methyl acrylate in aqueous solutions of ionic liquids such as [BMIM][BF<sub>4</sub>] [202] to give the Michael product in up to 96% yield (Scheme 5.2-81). Similar reactions are also described by Yadav in [BMIM][PF<sub>6</sub>] [203] where no catalyst is required. Unfortunately neither of these papers give an explanation of why the ionic liquids seem to catalyze the reaction.

In the Michael addition of azide ion to  $\alpha,\beta$ -unsaturated carbonyl compounds, Xia et al. found the reaction worked well with or without an amine base catalyst in up to 95% yield [204]. Two descriptions of the conjugate addition of thiols to alkenes were reported by Ranu [205] and Yadav [206]. Both authors found that thiols such as thiophenol add to cyclohexeneone in 92% yield in the ionic liquids [(C<sub>4</sub>H<sub>9</sub>)<sub>4</sub>N]Br or [BMIM][PF<sub>6</sub>] (Scheme 5.2-82).

An example of attaching a carbon nucleophile to an  $\alpha,\beta$ -unsaturated ketone is the Sakurai reaction. This involves the reaction of allyltrimethylsilane with an  $\alpha,\beta$ -unsaturated ketone to form a  $\delta,\epsilon$ -unsaturated ketone in the presence of a Lewis acid. Howarth used indium(III) chloride to catalyze this reaction in the ionic liquids [BMIM][BF<sub>4</sub>] and [BMIM][PF<sub>6</sub>] [207]. An example of this is shown in Scheme 5.2-83.

The L-proline catalyzed Michael reaction has been used in the synthesis of trifluoromethylated compounds as in Scheme 5.2-84 [208]. The yields in the reaction were in the 44–88% range and no diastereoselectivity was observed in the reaction.

A more detailed study of the diastereoselectivity of the Michael reaction was performed by Hagiwara et al. [209]. In the presence of a catalytic amount of optically



Scheme 5.2-84 The L-proline catalyzed Michael reaction in ionic liquids [208].

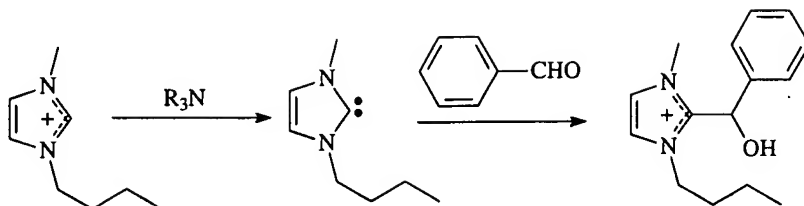


Scheme 5.2-85 The Baylis-Hillman reaction in ionic liquids [210].

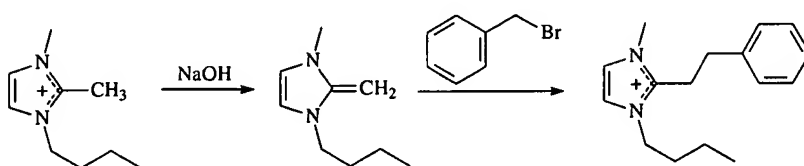
active pyrrolidine derivatives, derived from L-proline, the conjugate addition of an unmodified aldehyde to 3-buten-2-one in [BMIM][PF<sub>6</sub>] was achieved and afforded (2*S*)-5-keto-aldehyde in up to 59% *ee*. This reaction was also found to work for enamines derived from aldehydes and for nitroalkenes.

The Baylis-Hillman reaction involves the reaction of an aldehyde with an  $\alpha,\beta$ -unsaturated ketone in the presence of a tertiary amine. This results in the aldehyde adding at the  $\alpha$ -position of the carbon-carbon double bond. The reaction is conventionally carried out without a solvent; however this causes problems if the starting materials are solids. Hence the reaction was investigated in ionic liquids such as [BMIM][BF<sub>4</sub>] and [BMIM][PF<sub>6</sub>] [210]. The reaction of methyl acrylate with benzaldehyde proceeded 11 to 34 times faster in the ionic liquids than in the solvent acetonitrile. Various Lewis acidic additives had little effect on the reaction, with the exception of lithium perchlorate, which gave a 53 times rate enhancement. This reaction is shown in Scheme 5.2-85.

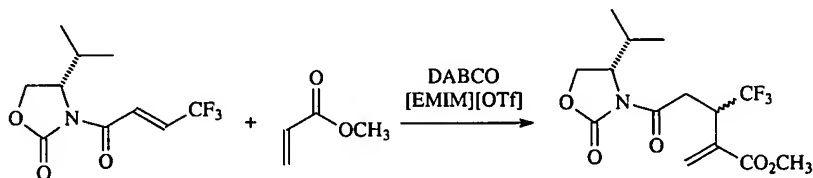
The same reactions were performed in a range of chloroaluminate(III) ionic liquids by Kumar [211]. By adjusting the aluminum chloride content from  $\chi = 0.45$  to  $\chi = 0.60$ , the rate of the reaction was found to increase from 3 to 20 times relative to a reaction in acetonitrile. A problem with this reaction is that the authors quenched the ionic liquid with sodium hydroxide solution which destroys the ionic liquid. This is usually because esters are notoriously difficult to extract from acidic chloroaluminate ionic liquids [73]. The Baylis-Hillman reaction was carried out in a range of neutral ionic liquids to determine which factors affected the reaction rate [212]. Keeping the [BMIM] cation constant, the anions were found to increase the reaction rate in the following order [OTf]<sup>−</sup> > [PF<sub>6</sub>]<sup>−</sup> > [N(Tf)<sub>2</sub>]<sup>−</sup> = [OAc]<sup>−</sup> > [BF<sub>4</sub>]<sup>−</sup> = [SbF<sub>6</sub>]<sup>−</sup>. Scandium(III) and lanthanum(III) triflate were found to enhance the reaction rate, with the lanthanum salt having the greatest effect. The reaction was also carried out in a range of phosphonium ionic liquids and was found to give improved yields compared with [BMIM][PF<sub>6</sub>] [213]. An explanation as to why the phosphonium ionic liquids gave better yields can be found in a paper



Scheme 5.2-86 The side reaction of imidazolium salts in the presence of a base [214].



Scheme 5.2-87 The reaction of 2-alkylimidazoles in the presence of base [215].



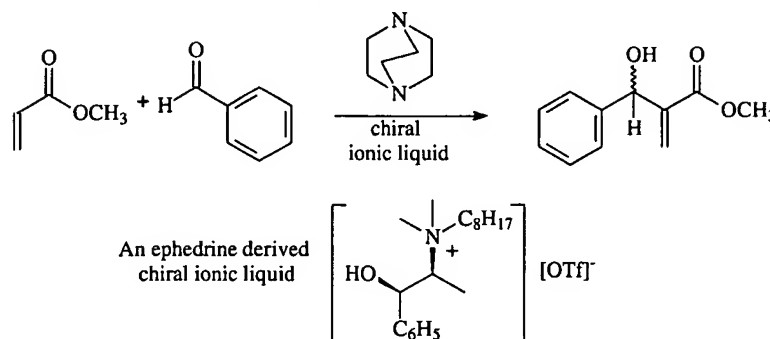
Scheme 5.2-88 A modified Baylis-Hillman reaction with a chiral auxiliary [216].

by Aggarwal et al. [214]. Imidazolium ionic liquids are not stable in the presence of moderate or strong bases. They undergo deprotonation at the 2-position to give a carbene, which can then react with the starting materials. This is shown in Scheme 5.2-86. It should also be mentioned that 1,2,3-trialkylimidazole cations are not stable in the presence of a base. An example of this is in the reaction of 1,2-dimethyl-3-butylimidazolium hexafluorophosphate with benzyl bromide using sodium hydroxide as a base [215]. Here the 2-methyl group reacts with the benzyl bromide to form a new benzylated ionic liquid. A plausible explanation is shown in Scheme 5.2-87. The main conclusion here is that imidazolium ionic liquids are not suitable for reactions involving bases.

The diastereoselectivity of the Baylis-Hillman reaction was investigated by attaching chiral auxiliaries to  $\alpha,\beta$ -unsaturated ketones [216]. The use of the 4-isopropylloxazolidinone chiral auxiliary in [EMIM][OTf] gave rise to very low diastereomer ratios (45:55) (Scheme 5.2-88). The authors also describe a proline-catalyzed aldol reaction of acetone, butanone, hydroxyacetone and chloroacetone with a chiral imine and obtain up to 9:1 diastereomer ratios.

A potentially very important use of chiral ionic liquids is their use in affecting the stereochemical outcomes of chemical reactions. This was demonstrated in





**Scheme 5.2-89** The use of a chiral ionic liquid in the Baylis-Hillman reaction [217].

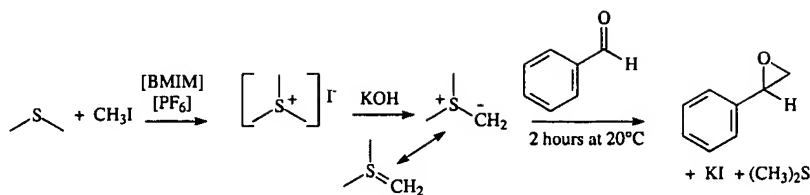
Baylis-Hillman reactions by Loupy et al. [217] (Scheme 5.2-89). Enantioselectivities in the 29–44 % range were obtained by varying the ionic liquid to starting material ratios from 0.5:1 to 3:1. The yields were in the range 65–88 % after 4 days at 30 °C.

#### 5.2.4.4 Methylene Insertion Reactions (Addition to C=O and C=C)

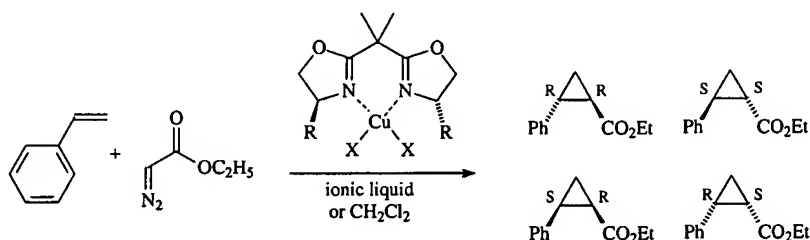
The first methylene insertion reaction in ionic liquids involves the reaction of a trialkyl sulfonium salt with an aldehyde to give an epoxide [4]. Here a sulfide is alkylated with methyl iodide to give a methylsulfonium iodide which adds the methylene group across an aldehyde double bond [218]. The ionic liquid chosen was [BMIM][PF<sub>6</sub>] and potassium hydroxide was used as a base. However, it is known that [BMIM][PF<sub>6</sub>] is not stable to KOH over the long term and a base stable ionic liquid would be preferred for this reaction. This is shown in Scheme 5.2-90. A more detailed description of methylene insertion reactions was described by Chandrasekhar et al. who also carried out the addition of trimethylsulfonium iodide to aldehydes in the same ionic liquid, and using the same base [219]. The addition of trimethylsulfonium iodide and trimethylsulfoxonium iodide to  $\alpha,\beta$ -unsaturated ketones also gave rise to addition on the alkene, to give a cyclopropane ring [219]. The addition of ethyldiazoacetate to styrene using a chiral bisoxazoline–copper(II) catalyst was investigated in four ionic liquids [220]. This is shown in Scheme 5.2-91. The reaction gave a roughly 2:1 *trans*- to *cis*- ratio and *ees* of the *cis* and *trans* isomers ranging from 2 to 94%. The advantage of the ionic liquids reaction compared with one in a molecular solvent is that the bisoxazoline catalyst could be recycled and reused. The effect of halide impurities in this cyclopropanation reaction was also investigated [221].

The first examples of Horner-Wadsworth-Emmons reactions have been given by Kitazume and Tanaka [222]. Here the ionic liquid [EtDBU][OTf], has been used in the synthesis of  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated esters (Scheme 5.2-92). It was found that when K<sub>2</sub>CO<sub>3</sub> was used as a base, the *E*-isomer was the major product whereas when DBU was used as a base, the *Z*-isomer was the major product. The reaction was

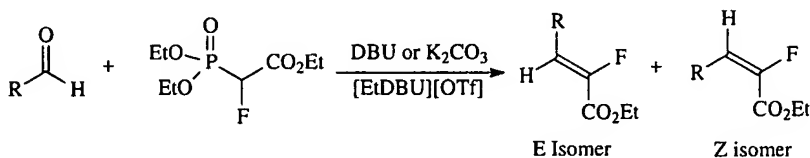
## 340 | 5 Organic Synthesis



Scheme 5.2-90 The sulfonium iodide prompted methylene addition to aldehydes [218, 219].



Scheme 5.2-91 The chiral copper(II)-catalyzed reaction of styrene and ethyl diazoacetate [220].



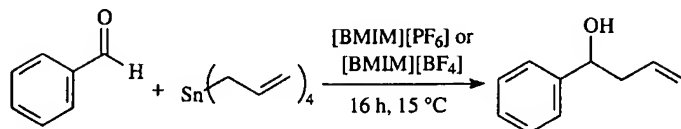
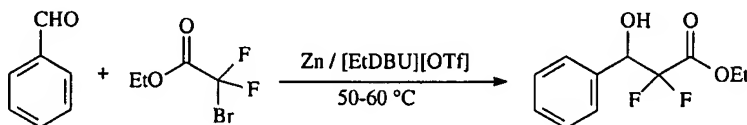
Scheme 5.2-92 The Horner-Wadsworth-Emmons reaction in an ionic liquid [222].

also performed in  $[\text{EMIM}][\text{BF}_4]$  and  $[\text{EMIM}][\text{PF}_6]$  but gave lower yields than with  $[\text{EtDBU}][\text{OTf}]$  [222].

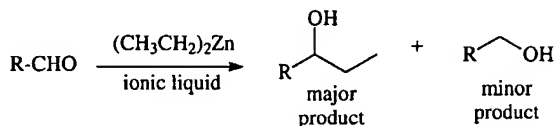
## 5.2.4.5 Addition Reactions Involving Organometallic Reagents

The addition of organometallic reagents to carbonyl compounds is an important reaction in organic chemistry, with the Grignard reaction being one example of this. Hence protocols that achieve similar results in ionic liquids are desirable. Gordon and McCluskey [223] have reported the formation of homoallylic alcohols, from the addition of allyl stannanes to aldehydes in the ionic liquids  $[\text{BMIM}][\text{BF}_4]$  and  $[\text{BMIM}][\text{PF}_6]$  (Scheme 5.2-93). It was found that the ionic liquid could be recycled and reused over several reaction cycles. When an imine formed from the aldehyde was substituted for the aldehyde, the nitrogen analog was formed. This variation was carried out in  $[\text{BMIM}][\text{BF}_4]$  and typically gave 82–93% yields [224].

Kitazume and Kasai have investigated the Reformatsky reaction in three ionic liquids. This involves the reaction of an  $\alpha$ -bromoester with zinc to give an  $\alpha$ -zinc bromide ester, which in turn reacts with an aldehyde to give an addition product. An example of this reaction is given in Scheme 5.2-94. Moderate to good yields

Scheme 5.2-93 Allylation of aldehydes in  $[\text{BMIM}][\text{PF}_6]$  or  $[\text{BMIM}][\text{BF}_4]$  [223].

Scheme 5.2-94 The Reformatsky reaction in ionic liquids [225].



Scheme 5.2-95 The addition of diethyl zinc to aldehydes [226].

(45–95%) were obtained in ionic liquids such as  $[\text{EtDBU}][\text{OTf}]$  for the reaction of ethylbromoacetate or ethylbromodifluoroacetate and benzaldehyde [225].

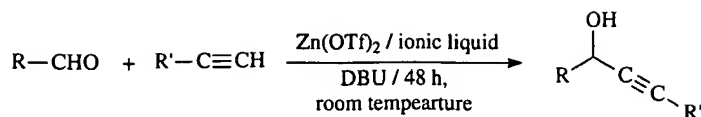
The ionic liquids,  $[\text{BMIM}][\text{Br}]$ ,  $[\text{BMIM}][\text{BF}_4]$ ,  $[\text{BMIM}][\text{PF}_6]$ ,  $[\text{BDMIM}][\text{BF}_4]$ , and  $[\text{BPY}][\text{BF}_4]$ , were examined as the solvent media for dialkylzinc addition to aldehydes giving the corresponding alcohols. The ionic liquid  $[\text{BPY}][\text{BF}_4]$  was found to be the solvent of choice, giving the best yields, and was found to be easily recovered and reused [226] (Scheme 5.2-95). It was found that the imidazolium salts react with diethyl zinc to form a carbene complex of zinc, but the 2-methylimidazolium or pyridinium salts did not react and hence could be recycled.

The reactions of aldehydes with alkynes to give propargyl alcohols are also described in Kitazume and Kasai's paper [226]. Here, various aldehydes such as benzaldehyde or 4-fluorobenzaldehyde were treated with alkynes such as phenylethyne or pent-1-yne in three ionic liquids:  $[\text{EtDBU}][\text{OTf}]$ ,  $[\text{BMIM}][\text{PF}_6]$  and  $[\text{BMIM}][\text{BF}_4]$  (Scheme 5.2-96). Both a base (DBU) and  $\text{Zn}(\text{OTf})_2$  were required for the reaction to be effective. The yields were in the 50–70% range. The best ionic liquid for this reaction depended on the individual reaction.

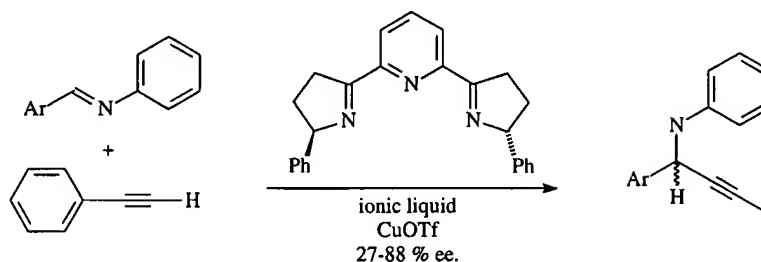
The enantioselective addition of alkynes to imines using a 2,6-bis(4-phenyloxazolino)pyridine catalyst was carried out by Rosa et al. to give a chiral amino alkyne (Scheme 5.2-97) [227]. The reaction gave similar yields and selectivities to the reaction in toluene, but the catalyst and ionic liquids could be recycled and reused.

McCluskey et al. have also used  $[\text{BMIM}][\text{BF}_4]$  as a solvent for the allylation of aldehydes and Weinreb amides [228]. Similar diastereoselectivities and similar or

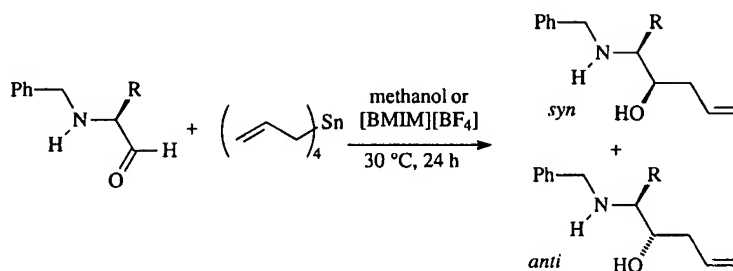
## 342 | 5 Organic Synthesis



**Scheme 5.2-96** The zinc triflate-catalyzed coupling of alkynes with aldehydes to give propargyl alcohols in an ionic liquid [226].



**Scheme 5.2-97** The chiral addition of an alkyne to an imine [227].

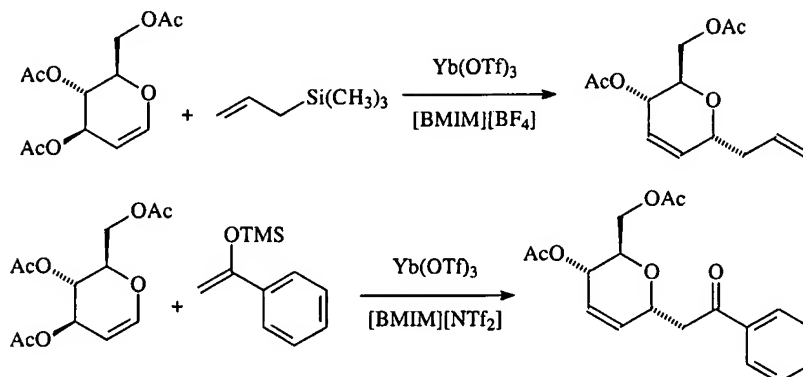


**Scheme 5.2-98** The reaction of tetraallylstannane with an aldehyde in methanol or [BMIM][BF<sub>4</sub>] [228].

slightly lower yields were obtained in this ionic liquid, compared with reactions carried out in methanol (Scheme 5.2-98, Table 5.2-5). The lower yield assigned to the reaction in the ionic liquid is thought to be due to difficulty in extracting the product from the ionic liquid.

**Table 5.2-5** The yields and selectivities for the reaction in Scheme 5.98 [228].

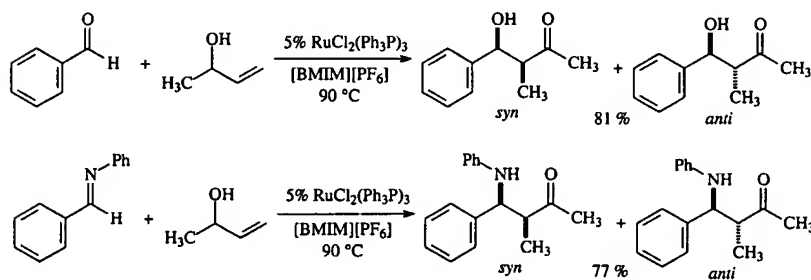
R	<i>syn</i> : <i>anti</i> -	Yield [BMIM][BF <sub>4</sub> ] (%)	Yield methanol (%)	<i>d.e.</i> (%)
CH <sub>3</sub>	82:18	72	87	64
CH(CH <sub>3</sub> ) <sub>2</sub>	93:7	70	74	86
PhCH <sub>2</sub>	93:7	73	82	86



**Scheme 5.2-99** The Carbon-Ferrier reaction in [BMIM][BF<sub>4</sub>] and [BMIM][PF<sub>6</sub>].

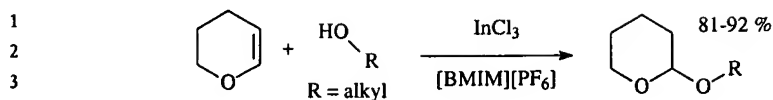
The Carbon-Ferrier reaction involves the addition of an allylsilane or silyl-enol ether to a dihydropyran. This was found to occur in the ionic liquids [BMIM][BF<sub>4</sub>] and [BMIM][NTf<sub>2</sub>] using Yb(OTf)<sub>3</sub> as a catalyst [229]. The reactions typically gave 80% yield for the reactions of allyl silanes and 60% yield for the reactions with TMS enol-ethers (Scheme 5.2-99).

The Mukaiyama aldol reaction involves the addition reaction of a TMS-enol ether to an aldehyde. Loh et al. have investigated the reaction of 1-methoxy-2-methyl-1-trimethylsiloxypropene with aliphatic and aromatic aldehydes in chloride, [BF<sub>4</sub>] and [PF<sub>6</sub>] ionic liquids. The yields varied considerably and it was found that the chloride ionic liquids gave the best yields (50–74%) [230]. Ruthenium complexes have been used in the addition of allyl alcohols to aldehydes and imines in [BMIM][PF<sub>6</sub>] [231] (and later in a very similar paper [232]). The addition of a co-catalyst such as indium(III) acetate was found to dramatically improve the yields in some cases and it was found that the ionic liquid/catalyst combination could be recycled. Examples of these reactions are shown in Scheme 5.2-100.



**Scheme 5.2-100** The addition of allyl alcohols to aldehydes and imines [231].

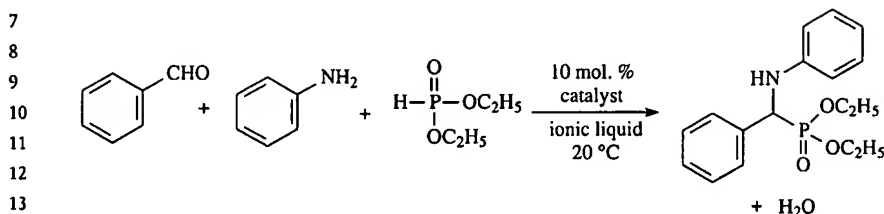
## 344 | 5 Organic Synthesis



5 Scheme 5.2-101 The tetrahydropyranylation of alcohols in [BMIM][PF<sub>6</sub>] [233].

6

7



15 Scheme 5.2-102 The three component reactions of benzaldehyde,  
16 aniline and diethyl phosphonate in ionic liquids, catalyzed by lanthanide  
17 triflates and indium(III) chloride [235].

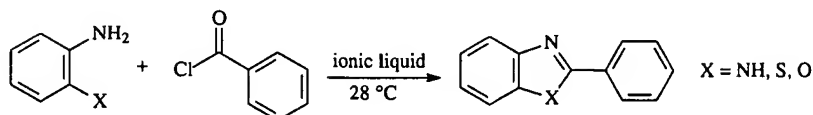
18

19 5.2.4.6 Miscellaneous Addition Reactions

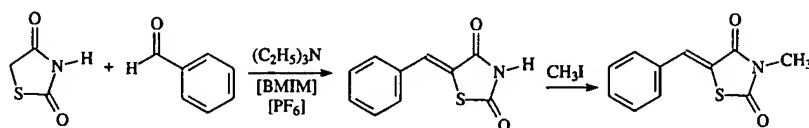
20 A common protecting group in organic chemistry is the tetrahydropyranyl group.  
21 Yadav found that a 5 mol% solution of indium(III) chloride in [BMIM][PF<sub>6</sub>] or  
22 [BMIM][BF<sub>4</sub>] catalyzed the addition of alcohols to the alkene in tetrahydropyran  
23 (Scheme 5.2-101) [233]. The reaction proceeded at ambient temperatures and in, typ-  
24 ically, 90% yield. The authors also claim that the reaction works well in [BMIM][BF<sub>4</sub>]  
25 and to a lesser extent in [BMIM][PF<sub>6</sub>] without the indium catalyst being present.  
26 As this reaction is well known to be catalyzed by traces of acid, and the [BF<sub>4</sub>]<sup>-</sup> and  
27 [PF<sub>6</sub>]<sup>-</sup> anions readily give traces of HF, it seems that it is the impurities in the ionic  
28 liquid that are promoting the reaction. Indium(III) bromide in [BMIM][PF<sub>6</sub>] was also  
29 found to catalyze the formation of 1,3-dioxanes from alkenes and paraformaldehyde  
30 [234].

31 Lee et al. have investigated the Lewis acid-catalyzed three-component synthesis of  
32 α-amino phosphonates [235]. This was carried out in the ionic liquids [BMIM][PF<sub>6</sub>],  
33 [BMIM][OTf], [BMIM][BF<sub>4</sub>] and [BMIM][SbF<sub>6</sub>], and the results were compared with a  
34 similar reaction carried out in dichloromethane (Scheme 5.2-102). Lee found that the  
35 reaction gave good yields (70–99%) in the ionic liquids [BMIM][PF<sub>6</sub>], [BMIM][OTf]  
36 and [BMIM][SbF<sub>6</sub>] with Lewis acids such as Yb(OTf)<sub>3</sub>, Sc(OTf)<sub>3</sub>, Dy(OTf)<sub>3</sub>, and  
37 InCl<sub>3</sub>. The reaction was also performed in [BMIM][PF<sub>6</sub>] or dichloromethane using  
38 Sm(OTf)<sub>3</sub> as the catalyst. The ionic liquid reaction gave a yield of 99% compared  
39 with 70% for the reaction in dichloromethane [235]. Amines readily add to aldehydes  
40 and ketones to form imines. The addition of amines to ethylacetoacetate or pentan-  
41 2,4-dione (acac) result in the formation of an enamine. This was carried out either  
42 under solvent-free conditions or in tetrabutylammonium bromide. The reaction in  
43 the ionic media generally gave better yields than in the solvent-free reaction [236].

44 The formation of benzimidazoles, benzoxazoles and benzthiazoles by the addition  
45 of 2-(NH<sub>2</sub>), 2-(OH) and 2-(SH) anilines to acyl chlorides in ionic liquids was studied



**Scheme 5.2-103** The formation of benzimidazoles, benzoxazoles and benzthiazoles in ionic liquids.



**Scheme 5.2-104** The aldol reaction of benzaldehyde with 1,3-thiazolidine-2,4-dione [241].

by Srinivasan et al. [237]. The ionic liquids chosen for the study were 1,3-dibutyl imidazolium  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $[\text{BF}_4]^-$ ,  $[\text{PF}_6]^-$  and  $[\text{ClO}_4]^-$  or 1-H-3-butylimidazolium  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $[\text{BF}_4]^-$ ,  $[\text{PF}_6]^-$  and  $[\text{ClO}_4]^-$ . The yields in the formation of benzimidazoles were in the 84–95% range and the 1-H-3-butylimidazoles gave slightly faster reaction rates. The yields and reaction times in the formation of benzoxazoles and benzthiazoles were similar. A second report of this reaction using 1-pentylimidazolium bromide as the solvent and an aldehyde instead of an acyl chloride was achieved using microwave heating [238]. Examples are shown in Scheme 5.2-103.

## 5.2.5

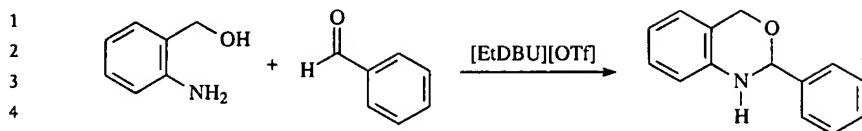
### Condensation Reactions

#### 5.2.5.1 General Condensation Reactions

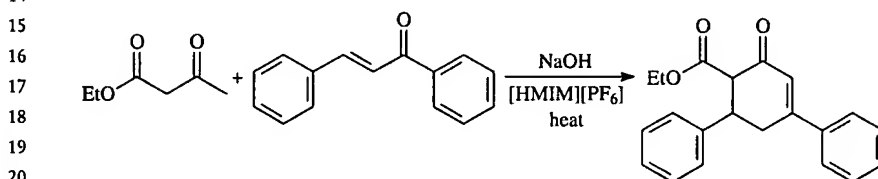
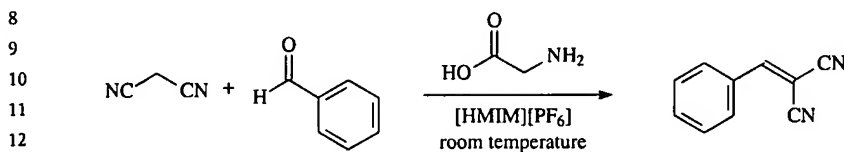
One of the simplest aldol condensations is the reaction of benzaldehyde with acetophenone. Iron(III) chloride hexahydrate in  $[\text{BMIM}][\text{BF}_4]$  catalyzes this reaction to give chalcone [239]. This same ionic liquid catalyst combination can also be used in the reaction of benzaldehyde with cyclopentanone and cyclohexanone [240]. The aldol reaction can also be base promoted in ionic liquids such as  $[\text{BMIM}][\text{PF}_6]$ . An example is the reaction of benzaldehyde with 1,3-thiazolidine-2,4-dione. The authors follow this reaction with methylation of the imide with methyl iodide (Scheme 5.2-104) [241].

Kitazume et al. have also investigated the use of  $[\text{EtDBU}][\text{OTf}]$  as a medium for the formation of heterocyclic compounds [242]. Compounds such as 2-hydroxymethylaniline readily condense with benzaldehyde to give the corresponding benzoxazine (Scheme 5.2-105). The product of the reaction is readily extracted with solvents such as diethyl ether and the ionic liquid can be recycled and reused. Thioacetals and dithianes formed from the condensation of 2-mercaptoethanol and ethane-1,2-dithiol with aldehydes also form readily in ionic liquids such as  $[\text{BMIM}][\text{BF}_4]$  at room temperature [243]. A large range of

## 346 | 5 Organic Synthesis



6 **Scheme 5.2-105** The formation of 2-phenylbenzoxazine in [EtDBU][OTf] [242].



22 **Scheme 5.2-106** The Knoevenagel condensation and Robinson annulation in [HMIM][PF<sub>6</sub>] [245].

23

24

25 thioacetalisation reactions were investigated by Patel et al. The ionic liquid chosen

26 was tetrabutylammonium tribromide, which was found to give the desired product

27 in catalytic quantities (0.02 eq.) [244].

28 Davis and coworkers have carried out the first examples of the Knoevenagel con-

29 densation and Robinson annulation reactions [245] in the ionic liquid [HMIM][PF<sub>6</sub>]

30 (HMIM = 1-hexyl-3-methylimidazolium) (Scheme 5.2-106). The Knoevenagel

31 condensation involved the treatment of propane-1,3-dinitrile with a base (glycine)

32 to generate an anion. This anion adds to benzaldehyde and, following loss of

33 a water molecule, gave 1,1-dicyano-2-phenylethene. The product was separated

34 from the ionic liquid by extraction with toluene. A similar set of Knoevenagel

35 condensation reactions catalyzed by an acetic acid – piperidine mixture in the ionic

36 liquid [BMIM][BF<sub>4</sub>] were described by Bao et al. This involved the condensation

37 of diethyl malonate and ethylcyanoacetate with salicylaldehyde [246]. Hydrotal-

38 cite (a hydrated magnesium–aluminum carbonate) was used in the reaction in

39 Scheme 5.2-106 and other Knoevenagel reactions in [BMIM][BF<sub>4</sub>] and [BMIM][PF<sub>6</sub>].

40 The reaction was also found to work in the absence of catalyst in 94–100% yield,

41 but gave lower reaction rates [247]. Ethylenediammonium diacetate (EDDA)

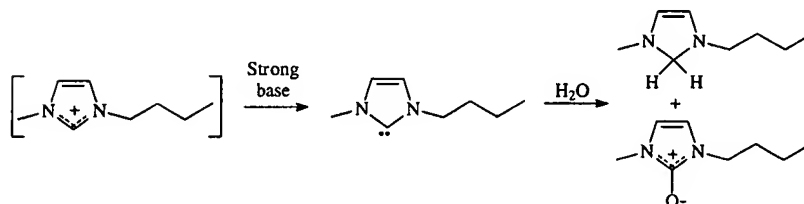
42 was used as a catalyst for the Knoevenagel condensation of benzaldehyde with

43 ethylacetoacetate or diethylmalonate in [BMIM][BF<sub>4</sub>] and [BMIM][PF<sub>6</sub>] [248]. With

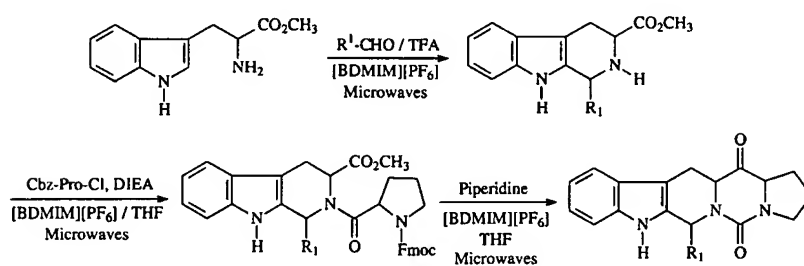
44 2-hydroxybenzaldehyde, a number of coumarins derivatives were synthesised in

45 90–93% yield. Ionic liquids such as [BPY][NO<sub>3</sub>], [BMIM][BF<sub>4</sub>] and [BMIM][PF<sub>6</sub>]





**Scheme 5.2-107** The disproportion of imidazolium cations under basic conditions [22, 215].



**Scheme 5.2-108** The microwave-assisted synthesis of indole alkaloids [251].

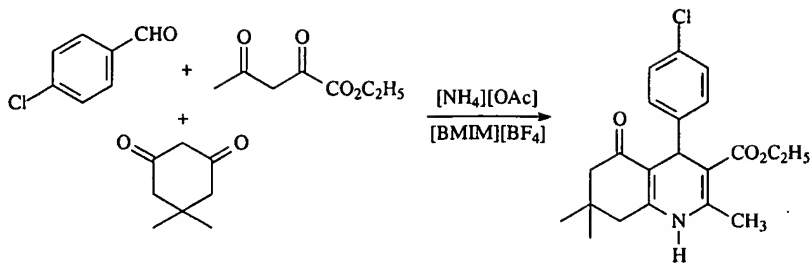
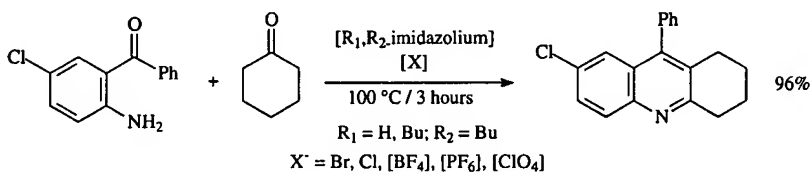
used as microwave absorbers were found to promote the Knoevenagel condensation [249]. The Robinson annulation of ethylacetoacetate and *trans*-chalcone proceeded smoothly to give 6-ethoxycarbonyl-3,5-diphenyl-2-cyclohexenone in 48% yield (Scheme 5.2-106) [245]. The product was separated from the ionic liquid by means of solvent extraction with toluene. In both these reactions, the ionic liquid [HMIM][PF<sub>6</sub>] was recycled and reused with no lowering of product yield.

The suitability of imidazolium ionic liquids as reaction media for the base-catalyzed Knoevenagel and Claisen reaction was investigated by Garcia et al. [250]. Indirect evidence for the formation of the carbene 1-methyl-3-butylimidazolyliene from [BMIM][PF<sub>6</sub>] was found and the authors postulate the formation of an imidazolium anion by hydride abstraction from 1,4-cyclohexadiene. This is an antiaromatic species and is previously unknown. A more plausible explanation is the disproportionation of the imidazolium cation via the carbene, shown in Scheme 5.2-107. [22, 215].

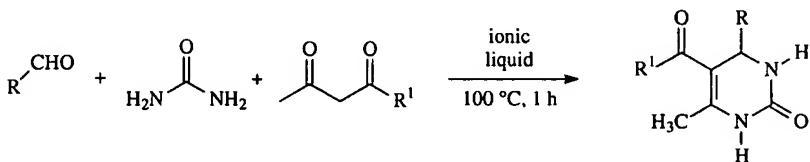
A range of microwave-assisted condensation reactions was used in the synthesis of indole alkaloids with pharmaceutical applications. An example is shown in Scheme 5.2-108 [251]. A one-pot synthesis of a pharmaceutically active compound was synthesized by a series of three condensation reactions in a range of [BF<sub>4</sub>] and [PF<sub>6</sub>] ionic liquids. This is shown in Scheme 5.2-109 [252].

A range of 1,3-dialkylimidazolium and 1-H-3-alkylimidazolium ionic liquids were used in the condensation of ketones with 2-aminoacetophenones to give quinolines [253] (the Friedlander annulation). The authors discuss how the basicity of the anion affects the reaction and an example is shown in Scheme 5.2-110. Deng and

## 348 | 5 Organic Synthesis

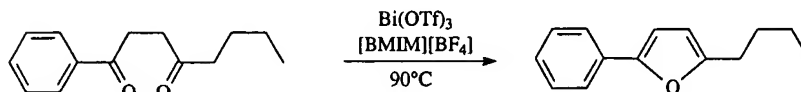
Scheme 5.2-109 The synthesis of polyhydroquinoline derivatives in [BMIM][BF<sub>4</sub>] [252].

Scheme 5.2-110 The Friedlander annulation in ionic liquids [253].

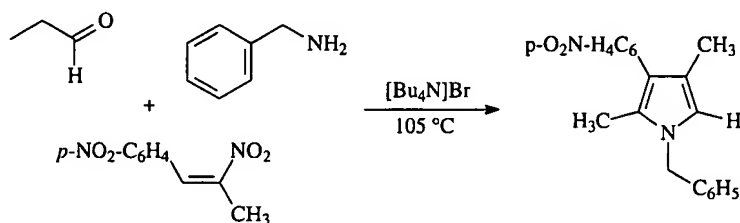
Scheme 5.2-111 The Biginelli reaction in an ionic liquid ( $R = \text{C}_6\text{H}_5$ ,  $4\text{-(H}_3\text{CO)C}_6\text{H}_4$ ,  $4\text{-Cl-C}_6\text{H}_4$ ,  $4\text{-(O}_2\text{N)C}_6\text{H}_4$ ,  $\text{C}_5\text{H}_{11}$ ;  $R^1 = \text{OC}_2\text{H}_5$ ,  $\text{CH}_3$ ) [254].

Peng have found that certain ionic liquids catalyze the Biginelli reaction [254]. Usually, this reaction is catalyzed by Lewis acids such as  $\text{InCl}_3$ ,  $[\text{Fe}(\text{H}_2\text{O})_6]\text{Cl}_3$ ,  $\text{BF}_3 \cdot \text{O}(\text{C}_2\text{H}_5)_2$ , or by acid catalysts such as Nafion-H. The reaction was found to give yields in the 77–99% range for the examples in Scheme 5.2-111 in the ionic liquids [BMIM][PF<sub>6</sub>] or [BMIM][BF<sub>4</sub>]. The reaction fails if there is no ionic liquid present or in the presence of tetrabutylammonium chloride. Peng et al. have also developed a method for the formation of triazines in [BMIM][PF<sub>6</sub>] using KOH as a catalyst [255]. The problem here is that both the [BMIM]<sup>+</sup> cation and the [PF<sub>6</sub>]<sup>−</sup> anion are unstable in the long term under the conditions employed in the reaction [215, 216].

1,4-Diketones condense to furans or pyrroles in the presence of a primary amine and an acidic catalyst. Yadav has carried out numerous such reactions in the ionic liquid [BMIM][BF<sub>4</sub>], using bismuth triflate as a catalyst [256]. The reaction typically gave 80–90% yield and the ionic liquid/catalyst was easily recycled (Scheme 5.2-112). With the addition of a primary amine to a 1,4-diketone, pyrroles can be formed.



**Scheme 5.2-112** The condensation of 1,4-diketones to furans in [BMIM][BF<sub>4</sub>] [256].



**Scheme 5.2-113** The three-component synthesis of pyrroles in [TBA]Br [258].

Yields in the 85–99% range were observed by Yang et al. [257] without the need for a catalyst.

The three-component condensation of an amine, aldehyde and nitroalkene to form substituted pyrroles was carried out in [TBA]Br [258]. No catalyst is required for this reaction and the [TBA]Br molten salt can be recycled. An example is shown in Scheme 5.2-113.

#### 5.2.5.2 The Mannich Reaction

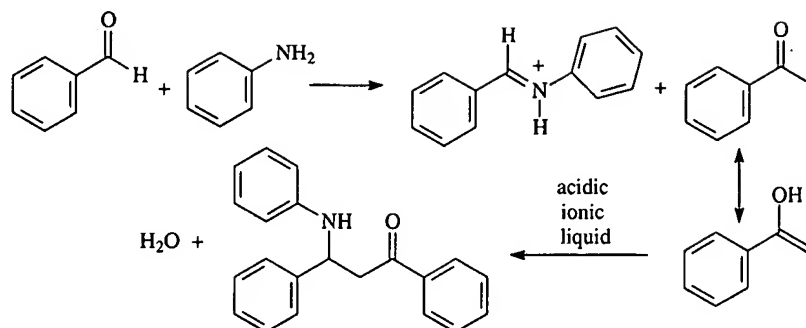
The Mannich reaction involves the condensation of an aldehyde or ketone with an iminium salt usually derived from formaldehyde or other aldehyde and an amine. An example is the use of four acidic ionic liquids in the reaction of benzaldehyde, aniline and acetophenone to give a  $\beta$ -amino ketone as in Scheme 5.2-114 [259].

A Mannich type reaction was used in the three-component synthesis of isoquinolic acids in [BMIM][BF<sub>4</sub>] or [BMIM][PF<sub>6</sub>] [260] (Scheme 5.2-115). These reactions are normally catalyzed by Lewis acids such as BF<sub>3</sub>–OEt<sub>2</sub>, TiCl<sub>4</sub> or SnCl<sub>4</sub>. The reaction in the ionic liquids does not require a catalyst to be added, although addition of 5 mol% of indium(III) chloride does marginally improve the yield (87–95%).

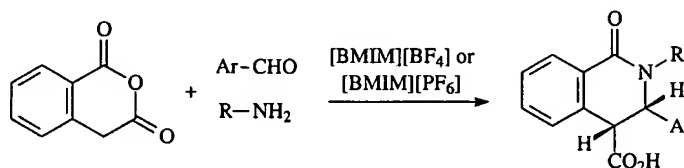
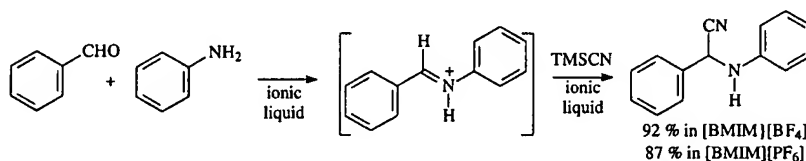
Another related reaction involves the addition of cyanide to an iminium ion formed from the reaction of an amine with an aldehyde. The use of ionic liquids such as [BMIM][BF<sub>4</sub>] gave significantly enhanced yields and reaction rates when compared to molecular solvents such as acetonitrile or dichloromethane [261]. This reaction is shown in Scheme 5.2-116.

Potassium alkynyltrifluoroborates react with amines and salicylaldehydes in the presence of benzoic acid to generate highly functionalized amines [262]. Ionic liquids such as [BMIM][BF<sub>4</sub>] are suitable solvents for the reaction. An example is shown in Scheme 5.2-117.

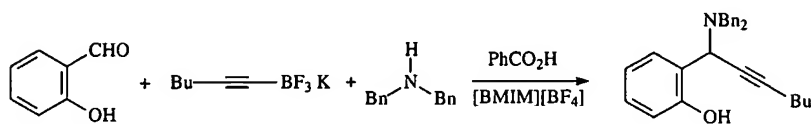
## 350 | 5 Organic Synthesis



Scheme 5.2-114 The Mannich reaction in acidic ionic liquids [259].

Scheme 5.2-115 The three-component synthesis of *cis*-isoquinolonic acids in ionic liquids [260].

Scheme 5.2-116 The addition of TMS cyanide to an iminium ion formed from the reaction of an amine with an aldehyde [261].

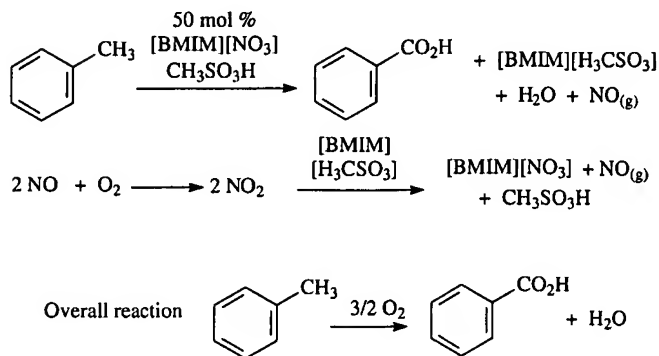
Scheme 5.2-117 The Mannich reaction with alkynyl borates in [BMIM][BF<sub>4</sub>] [262].

## 5.2.6

## Oxidation Reactions

## 5.2.6.1 Functional Group Oxidation Reactions

Ionic liquids have been used for a wide variety of oxidations, ranging from the relatively straightforward oxidation of alcohols to ketones, to the more difficult oxidations of alkanes. For clean synthesis, the oxidizing agent should give rise to



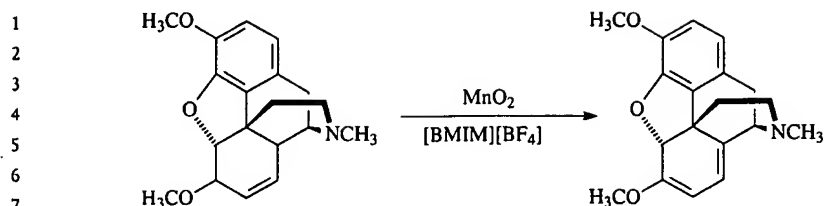
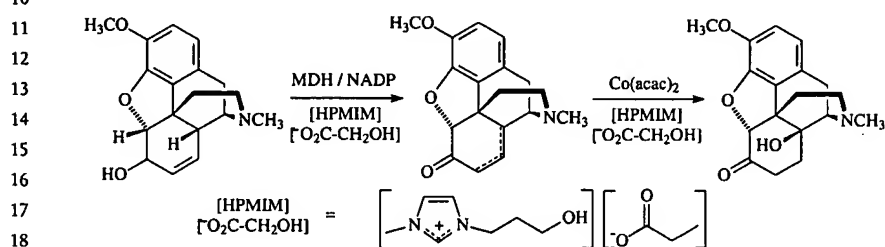
Scheme 5.2-118 The oxidation of toluene to benzoic acid with [BMIM][NO<sub>3</sub>] [263].

non-toxic by-products and ideally only have water as the by-product. In this respect the ideal oxidizing agents are oxygen (air) or hydrogen peroxide. Earle et al. have developed an oxidation of alkylaromatic compounds to the corresponding carboxylic acid or arylketone in nitrate ionic liquids (Scheme 5.2-118) [263].

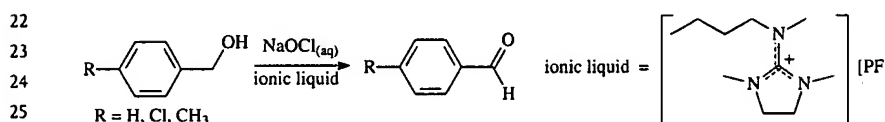
Singer and Scammells have investigated the  $\gamma$ -MnO<sub>2</sub> oxidation of codeine methyl ether (CME) to thebaine in the ionic liquid [BMIM][BF<sub>4</sub>] [264]. The ionic liquid was used in different ways and with mixed results (Scheme 5.2-119). For example, the oxidation of CME in the ionic liquid gave 38% yield after 120 h. A similar reaction under biphasic conditions (with diethyl ether) gave a 36% yield of thebaine. This reaction gave a 25% yield of thebaine when carried out in tetrahydrofuran (THF). The authors found that the yield could be increased to 95% by use of sonication of the reaction vessel. The ionic liquid was then used to extract the manganese by-products and impurities from an ethyl acetate solution of the product. A second paper describes the oxidation of codeine to oxycodone, in a two-stage process [265]. The first step is the oxidation of codeine with morphine dehydrogenase (MDA) and NADP (nicotinamide diphosphate) to a codeinone/neopinone mixture, followed by a cobalt(II) acetoacetate-catalyzed hydration to oxycodone. This is shown in Scheme 5.2-120. The ionic liquid chosen is 1-(3-hydroxypropyl)-3-methylimidazolium 2-hydroxyacetate. This shows much stronger hydrogen bonding than ionic liquids such as [BMIM][PF<sub>6</sub>] and is able to solubilise the opiates under investigation.

A straightforward oxidation of alcohols uses the readily available and cheap oxidant: sodium hypochlorite. A guanidinium ionic liquid was chosen for this reaction because of its greater stability, particularly under basic conditions [266]. Here, the ionic liquid acted as a phase transfer catalyst in the oxidation of benzyl alcohols to the corresponding aldehyde (Scheme 5.2-121). The guanidinium ionic liquid was recovered and found by NMR to be unchanged. Hypervalent iodine reagents were effective in the oxidation of alcohols to ketones in ionic liquids. The reaction simply involves stirring the hypervalent iodine reagent with an alcohol in the ionic liquid at room temperature, followed by extracting the aldehyde or ketone product

## 352 | 5 Organic Synthesis

Scheme 5.2-119 The oxidation of CME to thebaine in [BMIM][BF<sub>4</sub>] [264].

Scheme 5.2-120 The preparation of oxycodone from codeine in an ionic liquid [265].



Scheme 5.2-121 The NaOCl oxidation of alcohols to aldehydes [266].

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with diethyl ether as in Scheme 5.2-122 [267]. Another way of oxidising alcohols to aldehydes or ketones is with hydrogen peroxide in [BMIM][BF<sub>4</sub>] [268]. A catalyst is required and [BMIM][W<sub>10</sub>O<sub>23</sub>] proved effective in this task. The yields are quantitative and the selectivity for the aldehyde (over the carboxylic acid) is >95%.

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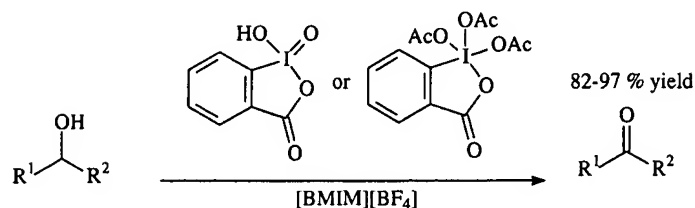
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A more challenging oxidation reaction is the conversion of alkanes to alcohols or ketones. [BMIM][PF<sub>6</sub>] has been used as part of a solvent (dichloromethane, acetonitrile or dichloroethane are the other components) for manganese porphyrins which catalyze the phenyliodoso diacetate (PhI(OAc)<sub>2</sub>) oxidation of cyclic alkanes such as cyclohexane, adamantane or tetralin [269]. The reactions gave yields in the 25–55% range, based on the starting alkane. A number of pyridinium ionic liquids were found to be stable to superoxide ion and were used in the functionalization of siloxanes [270]. This involved the electrochemical reduction of dioxygen to superoxide ion. This in turn was used to activate hexamethyldisiloxane and add trimethylsiloxy groups to Ph<sub>2</sub>Si(OCH<sub>3</sub>)<sub>2</sub> or NC(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>SiCl<sub>2</sub>.

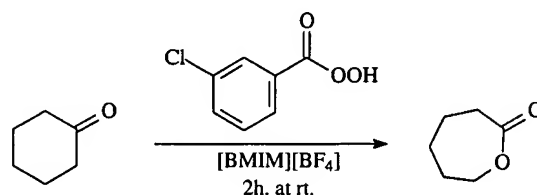
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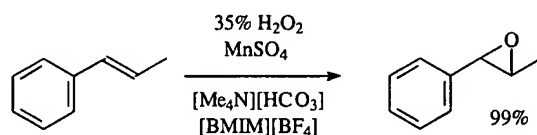
Yadav et al. have also carried out a range of Baeyer-Villiger oxidations in [BMIM][BF<sub>4</sub>]. This involves the reaction of a peracid; in this case *meta*-



Scheme 5.2-122 Hypervalent iodine oxidations in [BMIM][BF<sub>4</sub>] [267].



Scheme 5.2-123 The Baeyer-Villiger oxidation in [BMIM][BF<sub>4</sub>] [271].



Scheme 5.2-124 The epoxidation of *trans*-1-phenylprop-1-ene with 35% H<sub>2</sub>O<sub>2</sub> [272].

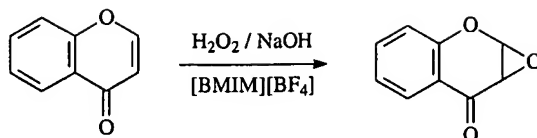
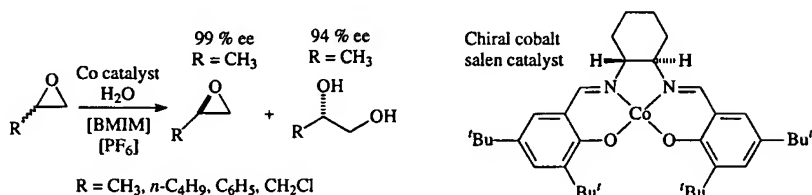
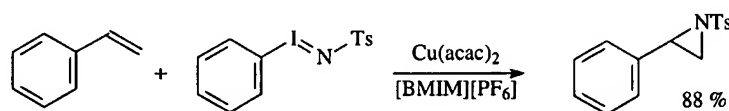
chloroperbenzoic acid with a ketone and results in the insertion of an oxygen atom  $\alpha$ - to the ketone [271]. An example of this is shown in Scheme 5.2-123.

#### 5.2.6.2 Epoxidation and Related Reactions

Numerous epoxidation reactions have been carried out in ionic liquids. One of the simplest uses hydrogen peroxide in [BMIM][BF<sub>4</sub>] with tetramethylammonium bicarbonate and manganese(II) sulfate as a catalyst [272]. The reaction was successful (typically 98–99%) various styrenes, cyclooctene, norbornene and pinene and the ionic liquid could be recycled and reused (Scheme 5.2-124).

A series of room-temperature ionic liquids were tested as solvents for dioxomolybdenum(VI) complexes in the catalytic epoxidation of *cis*-cyclooctene, using *tert*-butyl hydroperoxide (TBHP) as the oxygen source [273]. In general, the best results were obtained using the ionic liquid [BMIM][NTf<sub>2</sub>]. Upon addition of cyclooctene and TBHP (in decane) to solutions of MoO<sub>2</sub>X<sub>2</sub>(*p*-tolyl-(CH<sub>3</sub>-DAB)) [X = Cl, Me; *p*-tolyl-(CH<sub>3</sub>-DAB) = *N,N*-*p*-tolyl-2,3-dimethyl-1,4-diazabutadiene] in [BMIM][NTf<sub>2</sub>], biphasic mixtures were obtained. The epoxidation reactions proceeded with 100% selectivity to cyclooctene oxide, but activities were lower than those observed for the same catalysts in the absence of any additional solvent (other than decane). Another class of metal complexes that promote the epoxidation of alkenes are manganese(III)

## 354 | 5 Organic Synthesis

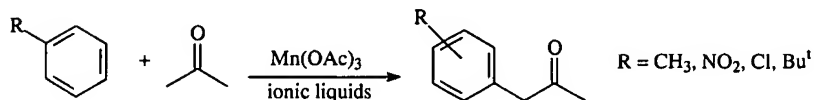
Scheme 5.2-125 Epoxidation reactions in  $[\text{BMIM}][\text{BF}_4]$  with alkaline  $\text{H}_2\text{O}_2$  [275].Scheme 5.2-126 The kinetic resolution of racemic epoxides in  $[\text{BMIM}][\text{PF}_6]$  or  $[\text{BMIM}][\text{NTf}_2]$  [276].Scheme 5.2-127 The aziridination of alkenes in  $[\text{BMIM}][\text{PF}_6]$  [277].

porphyrins. These complexes in  $[\text{BMIM}][\text{PF}_6]$  catalyzed the epoxidation of simple alkenes with hypervalent iodine reagents such as  $\text{Ph-IO}$  or  $\text{PhI}(\text{OAc})_2$  [274].

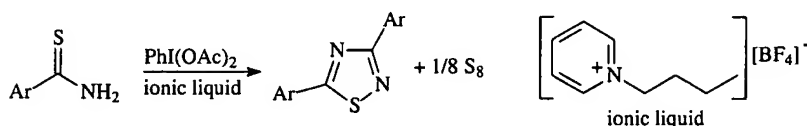
A convenient and efficient procedure for the epoxidation of chromone, isoflavone, and chalcone derivatives using  $[\text{BMIM}][\text{BF}_4]$  as solvent and alkaline hydrogen peroxide as oxidant was developed. The reactions proceed in good yields and faster than in conventional solvents. No evidence of formation of compounds derived from the opening of the epoxide ring was observed [275]. An example is shown in Scheme 5.2-125. A very similar alkaline hydrogen peroxide epoxidation in  $[\text{BMIM}][\text{PF}_6]$  is also described [276]. In the chiral  $\text{Co}(\text{III})(\text{salen})$ -catalyzed hydrolytic kinetic resolution of racemic epoxides, in the presence of ionic liquids, a  $\text{Co}(\text{II})(\text{salen})$  complex is oxidized to catalytically active  $\text{Co}(\text{III})(\text{salen})$  complex. During the reaction this oxidation state is stabilized against reduction to a  $\text{Co}(\text{II})$  complex which enables the reuse of the recovered catalyst for consecutive reactions without extra reoxidation. This is shown in Scheme 5.2-126.

The nitrogen equivalent of the epoxidation reaction is the aziridination reaction.  $\text{Cu}(\text{acac})_2$  was used as a catalyst for the aziridination of alkenes with  $N-(p\text{-tolylsulfonyl})\text{iodine}$  ( $\text{PhI}=\text{NTs}$ ) in  $[\text{BMIM}][\text{PF}_6]$  [277] and is shown in Scheme 5.2-127.





**Scheme 5.2-128** The coupling of acetone substituted benzenes in ionic liquids using ultrasound [278].



**Scheme 5.2-129** The oxidative dimerisation of thioamides [281].

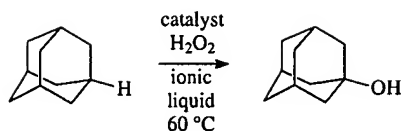
### 5.2.6.3 Miscellaneous Oxidation Reactions

The oxidative coupling of acetone with monosubstituted benzenes, promoted by manganese(III) acetate in three ionic liquids proceeded using ultrasound irradiation [278]. The reactions in the ionic liquids gave far better yields and improved selectivity for the *para*-isomer than similar reactions in acetic acid. This is shown in Scheme 5.2-128.

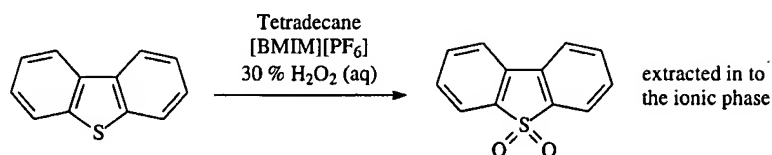
The oxidative dimerization of terminal alkynes with oxygen using a TMEDA/CuCl catalyst (the Glaser oxidation) was carried out in [BMIM][PF<sub>6</sub>] and [BMIM][BF<sub>4</sub>] [279]. The ionic liquid/catalyst mixture was recyclable (up to 6 times) and typical yields were in the 85–95% range, for 14 separate terminal alkynes. The oxidative coupling of 2-naphthols with iron(III) and copper(II) binary ionic liquids and solutions of iron(III), ruthenium(III) and copper(II) in [BMIM][PF<sub>6</sub>] were examined [280]. The reactions in the ionic liquids gave a marginal increase in yield over reactions in chlorobenzene or toluene. Phenyliodine(III) diacetate in butylpyridinium tetrafluoroborate promotes the dimerization of thioamides as in Scheme 5.2-129 [281]. This reaction gave 85–93% yields after 15 min at 75 °C. The product was extracted from the ionic liquid and the sulfur was removed by filtration. The yield remained the same when the ionic liquid was reused.

An important class of reactions is the remote functionalization of alkanes. An efficient C–H insertion reaction of H<sub>2</sub>O<sub>2</sub> into hydrocarbons by homogeneous methyltrioxorhenium(VII) (MTO), heterogeneous poly(4-vinylpyridine)/methyltrioxorhenium (PVP/MTO) and microencapsulated polystyrene/methyltrioxorhenium (PS/MTO) systems in ionic liquids, has been developed (Scheme 5.2-130). In some cases higher activity was observed when compared with the same reaction in molecular solvents. The heterogeneous catalysts are stable systems under the reaction conditions and can be recycled for more transformations [282].

The hydroxylation of benzene to give phenol was carried out using a biphasic mixture of hydrophobic ionic liquids such as [OMIM][BF<sub>4</sub>] or [OMIM][PF<sub>6</sub>] and water/hydrogen peroxide [283]. A range of transition metal dodecylsulfate catalysts were employed with the iron giving the best results. Conversions of benzene to phenol of 54% were obtained and the ionic liquid/catalyst combination could be



**Scheme 5.2-130** The oxidation of adamantane with  $\text{H}_2\text{O}_2$  [282].



**Scheme 5.2-131** The oxidative extraction of dibenzothiophene with  $[\text{BMIM}][\text{PF}_6]$  [284].

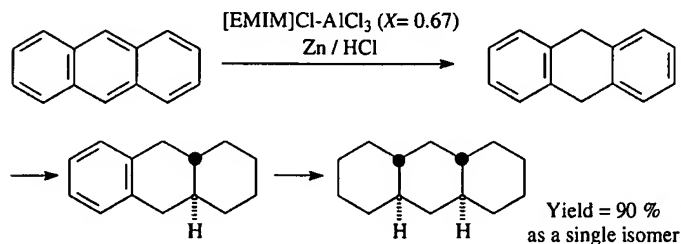
recycled. The desulfurisation of oils is a reaction of increasing importance as a means of reducing the amount of sulfur dioxide in the environment. Generally this involves oxidising the sulfur compounds to sulfones and extracting them with polar solvents such as dimethylsulfoxide. The oxidation of dibenzothiophene with hydrogen peroxide was carried out in biphasic or triphasic tetradecane/ionic liquid mixture/aqueous hydrogen peroxide [284]. The best desulfurisation process involved extracting dibenzothiophene from tetradecane with  $[\text{BMIM}][\text{PF}_6]$  and aqueous  $\text{H}_2\text{O}_2$  in a triphasic mixture. This is shown in Scheme 5.2-131.

### 5.2.7

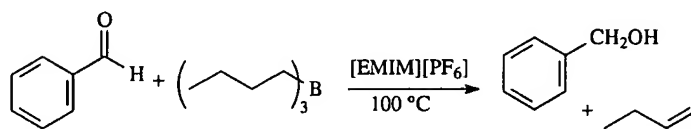
#### Reduction Reactions

Polycyclic aromatic hydrocarbons dissolve in chloroaluminate(III) ionic liquids to give brightly colored solutions (thought to be due to the protonated aromatic compound [285]). The addition of a reducing agent (such as an electropositive metal and a proton source) results in the selective hydrogenation of the aromatic compound. For example pyrene and anthracene can be reduced to perhydropyrene and perhydroanthracene at ambient temperatures and pressures (Scheme 5.2-132). Interestingly, only the thermodynamically most stable isomer of the product is obtained [286]. This contrasts with catalytic hydrogenation reactions, which require high temperatures and pressures and an expensive platinum oxide catalyst and give rise to an isomeric mixture of products.

Ionic liquids such as  $[\text{BMIM}][\text{BF}_4]$  and  $[\text{EMIM}][\text{PF}_6]$  have been used in the trialkylborane reduction of aldehydes to alcohols (Scheme 5.2-133) [287]. In the reduction of benzaldehyde with tributylborane, similar yields (90–96%) were obtained for the ionic liquids  $[\text{EMIM}][\text{BF}_4]$ ,  $[\text{EMIM}][\text{PF}_6]$ ,  $[\text{BMIM}][\text{BF}_4]$ , and  $[\text{BMIM}][\text{PF}_6]$ . The effect of electron-releasing and electron-withdrawing groups on the aromatic aldehyde were investigated. In general, electron-withdrawing groups such as halogen give near quantitative yields, but electron-releasing groups such as methoxy reduce the reaction rate and yield.



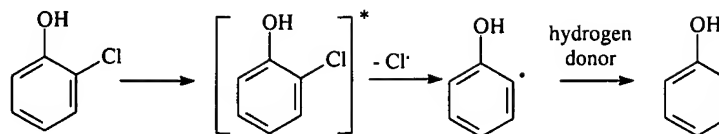
Scheme 5.2-132 The reduction of anthracene to perhydroanthracene [286].



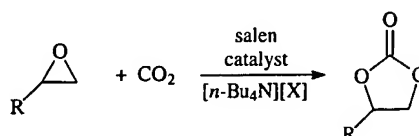
Scheme 5.2-133 The reduction of benzaldehyde in  $[\text{EMIM}][\text{PF}_6]$  [287].

This reduction is conventionally affected by reaction of an aldehyde or ketone with sodium borohydride in a solvent bearing an acidic proton such as methanol. In the first reported sodium borohydride reduction Howarth et al. found that the reduction of aldehydes and ketones with  $\text{NaBH}_4$  in the ionic liquid  $[\text{BMIM}][\text{PF}_6]$  can be achieved [288]. The ionic liquid can be recycled, and in some cases the product alcohol may be distilled directly from the ionic liquid eliminating classical organic solvents entirely. In a later example, sodium borohydride was also used to reduce aldehydes and ketones in a range of ionic liquids such as  $[\text{BMIM}][\text{BF}_4]$ ,  $[\text{C}_6\text{MIM}]\text{Br}$ ,  $[\text{EMIM}][\text{F}_3\text{CCO}_2]$  [289]. With  $\alpha,\beta$ -unsaturated ketones, the carbonyl was reduced and not the alkene group. Nitro groups readily undergo reduction to amino groups. Usually this is carried out using a tin(II) reagent or zinc in acetic acid. Tin(II) chloride was found to give this reaction in tetrabutylammonium bromide at  $90^\circ\text{C}$  [290]. This procedure gave lower reaction times, but the author does not discuss the recovery of the ionic liquid and the removal of the tin(IV) salts. The reduction of both carbonyl and nitro groups was achieved using a mixture of  $[\text{BMIM}][\text{PF}_6]$  and water [291]. These were biphasic reactions, and the ionic liquid could be recycled and reused. The sodium and borate salt by-products could be removed in the aqueous layer. The photochemical reduction of chlorinated phenols was carried out in  $[\text{BMIM}][\text{PF}_6]$  as in Scheme 5.2-134 [292]. Using 253.7 nm irradiation, the authors propose that a chlorine atom is lost and the phenol radical picks up a hydrogen atom from the solvent. The stability of the ionic liquid was investigated and it was found impurities hindered the regeneration of the ionic liquid. The reaction rate diminished to a small extent when the ionic liquid was recycled. The cobalt(I) salen complex has been used in a similar reaction: the debromination of cyclic *vic*-dibromides in ionic liquids using an electrochemical technique (cyclic voltammetry) [293] and dechlorination [294]. The work-up after electrolysis in the ionic liquid proved to be much simpler

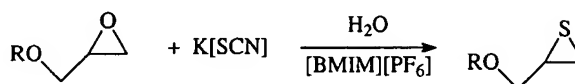
## 358 | 5 Organic Synthesis



Scheme 5.2-134 The photochemical reduction of 2-chlorophenol to phenol in [BMIM][PF<sub>6</sub>] [292].



Scheme 5.2-135 The fixation of carbon dioxide in the form of carbonates [296].



Scheme 5.2-136 The conversion of epoxides to thiiranes in [BMIM][PF<sub>6</sub>] [297].

than that in organic solvents, and the possibility of reuse of the ionic liquid was demonstrated. The related electrochemical dechlorination is also described and explanations are offered for factors affecting this reaction [295].

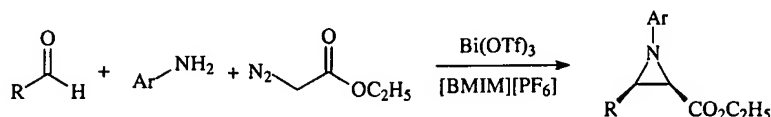
## 5.2.8

## Miscellaneous Reactions in Ionic Liquids

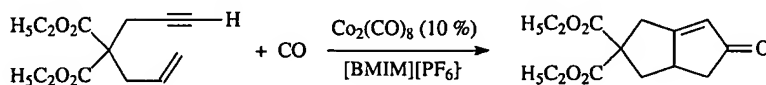
The chemical fixation of carbon dioxide to cyclic carbonates proceeds effectively under mild conditions using a bifunctional nucleophile–electrophile catalyst system. This was based on tetradentate Schiff-base aluminum complexes [(Salen)AlX] in conjunction with a quaternary ammonium salt [Bu<sub>4</sub>N][Y]. The electrophilicity of the central Al<sup>3+</sup> ion and the steric factor of the substituent groups on the aromatic rings of the (Salen)AlX (electrophile), and nucleophilicity and leaving ability of the anion [Y]<sup>−</sup> of [n-Bu<sub>4</sub>N][Y] (nucleophile) had a significant effect on the catalytic activity of the catalyst [296] (Scheme 5.2-135).

A variety of epoxides react with potassium thiocyanate in a [BMIM][PF<sub>6</sub>]/water mixture (2:1) at room temperature under mild conditions to produce the corresponding thiiranes in high yields. Enhanced rates and improved yields were observed in ionic liquids [297] (Scheme 5.2-136).

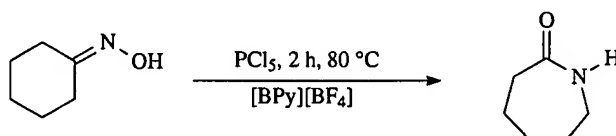
The imines formed from aldehydes and primary amines were converted to aziridines with ethyldiazoacetate in [BMIM][PF<sub>6</sub>] [298]. The catalyst employed was Bi(OTf)<sub>3</sub> and the *cis*-isomer was formed predominantly in 75–90% yield (Scheme 5.2-137).



Scheme 5.2-137 The three-component synthesis of aziridines in [BMIM][PF<sub>6</sub>] [298].



Scheme 5.2-138 The Pauson–Khand annulation in [BMIM][PF<sub>6</sub>] [300].



Scheme 5.2-139 The Beckmann rearrangement in ionic liquids [301].

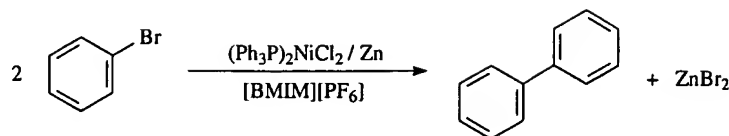
Ionic liquids ([BMIM][PF<sub>6</sub>]) are suitable media for the Co<sub>2</sub>(CO)<sub>8</sub>-catalyzed intramolecular and intermolecular Pauson–Khand annulation, provided that the reaction is carried out under a CO pressure of 10 bar [299]. Two diethyl allyl propargyl malonates were quantitatively converted into the relevant cyclopentenones, whereas heteroatom tethered enynes gave lower yields in their cyclocarbonylation products. An example is shown in Scheme 5.2-138. The reaction also works with the direct addition of ethyldiazoacetate to imines in [BMIM][BF<sub>4</sub>] and [BMIM][PF<sub>6</sub>] [300].

Beckmann rearrangements of several ketoximes were performed in the room-temperature ionic liquid based on 1,3-dialkylimidazolium or alkylpyridinium salts containing phosphorus compounds (e.g. PCl<sub>5</sub>) by Deng and Peng [301] (Scheme 5.2-139). Turnover numbers of up to 6.6 were observed, but the authors did not mention whether the ionic liquid could be reused.

A way of forming cyclic amides is by the reaction of a primary amine with a cyclic anhydride to give an imide. Chen et al. has carried out numerous of these reactions in [BMIM][PF<sub>6</sub>] to give the cyclic imide in 91–98% yield [302]. Howarth et al. have achieved the coupling of aryl halides with a zinc metal reducing agent in the ionic liquid [BMIM][PF<sub>6</sub>]. In this reaction, a zero-valent nickel catalyst (or coupling agent) is generated *in situ* from zinc and (Ph<sub>3</sub>P)<sub>2</sub>NiCl<sub>2</sub> [303] (Scheme 5.2-140).

A novel use of the salt [BMIM][PF<sub>6</sub>] is to enhance microwave absorption and hence accelerate the rate of a reaction. Ley found that [BMIM][PF<sub>6</sub>] enhanced the rate of the microwave promoted thionation of amides using a polymer supported thionating agent [304]. Hardacre et al. have developed a protocol for the synthesis of deuterated imidazoles and imidazolium salts [305]. The procedure involves the platinum- or palladium-catalyzed deuterium exchange of 1-methyl-d<sup>3</sup>-imidazole with D<sub>2</sub>O to give 1-methylimidazole-d<sup>6</sup>, followed by reaction with a deuterated alkyl halide.

## 360 | 5 Organic Synthesis



Scheme 5.2-140 The zinc promoted coupling of aryl halides [303].

Finally, a word of caution when using  $[\text{BF}_4]^-$  and  $[\text{PF}_6]^-$  ionic liquids – they are not stable and give off HF, particularly when heated in the presence of a proton source or a metal salt [21]. There are many examples of this in this chapter. An example of HF-catalyzed reactions is as follows: ether formation from alcohols is a classic acid-catalyzed reaction. An ether formation reaction was found to occur in a range of  $[\text{BF}_4]^-$  ionic liquids, with an example being the addition of methanol to *tert*-butanol to form methyl-*tert*-butyl ether (MTBE) [306]. The author is of the opinion that  $[\text{BF}_4]^-$  ionic liquids (even hydrophobic ones) can dehydrate alcohols to ether and refers to these ionic liquids as dehydrators. All that is happening here is a simple HF-catalyzed reaction. With many authors not aware of this phenomenon, they resort to all kinds of inappropriate explanations for what is occurring.

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## 364 | 5 Organic Synthesis

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### 5.3 Transition Metal Catalysis in Ionic Liquids

Peter Wasserscheid, Peter Schulz

Many transition metal complexes dissolve readily in ionic liquids, which enables their use as solvents for transition metal catalysis. Sufficient solubility for a wide range of catalyst complexes is an obvious, but not trivial, prerequisite for a versatile solvent for homogenous catalysis. Some of the other approaches to replace tradi-

tional volatile organic solvents in transition metal catalysis by “greener” alternatives, such as the use of supercritical CO<sub>2</sub> or perfluorinated solvents, suffer very often from low catalyst solubilities. This limitation is usually overcome by special ligand systems that have to be synthesized prior to the catalytic reaction.

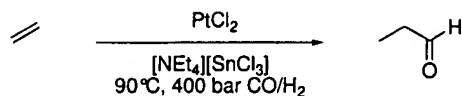
In the case of ionic liquids, a special ligand design is usually not necessary to get catalyst complexes dissolved in the ionic liquid in a sufficiently high concentration. However, it should be mentioned that sometimes the dissolving of a solid, crystalline complex in an (often relatively viscous) ionic liquid can be slow. This is due to restricted mass transfer and can be speeded up by either increasing the exchange surface (ultrasonic bath) or by lowering the ionic liquid's viscosity. The latter is easily achieved by adding small amounts of a volatile organic solvent that dissolves both the catalyst complex and the ionic liquid. As soon as the solution is homogeneous the volatile solvent is then removed *in vacuo*.

Even if no special ligand design is usually required to dissolve transition metal complexes in ionic liquids, the application of an ionic or highly polar ligand is usually required to immobilize the catalyst in the ionic medium. Particularly for continuous catalytic operation, where the ionic catalyst layer is intensively extracted with the non-miscible product phase, it is important to make sure that the amount of catalyst washed from the ionic liquid is extremely low. The full immobilization of the (often quite expensive) transition metal catalyst combined with the possibility of its recycle is usually a crucial criterion for the large-scale use of homogeneous catalysis (for more details see Section 5.4).

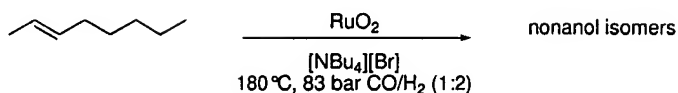
The first example of homogeneous transition metal catalysis in an ionic liquid was the platinum catalyzed hydroformylation of ethene in tetraethylammonium trichlorostannate (mp. 78 °C), described by Parshall in 1972 (Scheme 5.3-1(a)) [1]. In 1987, Knifton reported the ruthenium- and cobalt-catalyzed hydroformylation of internal and terminal alkenes in molten [Bu<sub>4</sub>P]Br, a salt that falls within the now accepted definition for an ionic liquid (see Scheme 5.3-1(b)) [2]. The first applications of room-temperature ionic liquids in homogeneous transition metal catalysis were described in 1990 by Chauvin et al. and by Wilkes et al.. Wilkes et al. used weakly acidic chloroaluminate melts and studied therein ethylene polymerization with Ziegler-Natta catalysts (Scheme 5.3-1(c)) [3]. Chauvin's group dissolved nickel catalysts in weakly acidic chloroaluminate melts and investigated the resulting ionic catalyst solutions for the dimerization of propene (Scheme 5.3-1(d)) [4].

The potential of ionic liquids as novel media for transition metal catalysis received a substantial boost by the work of Wilkes' group when they described, in 1992, the synthesis of non-chloroaluminate, room-temperature liquid systems with significantly enhanced stability to hydrolysis, e.g. low melting tetrafluoroborate melts [5]. In contrast to chloroaluminate ionic liquids, these “second generation ionic liquids” offer high tolerance to functional groups, which opens up a much larger range of applications for transition metal catalysis. The first successful catalytic reactions in ionic liquids with tetrafluoroborate ions included the rhodium catalyzed hydrogenation and hydroformylation of olefins [6]. Nowadays, tetrafluoroborate and (the slightly later published [7]) hexafluorophosphate ionic liquids are among the “work horses” for transition metal catalysis in ionic liquids. They combine – as some other

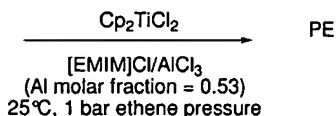
a) Parshall (1972):



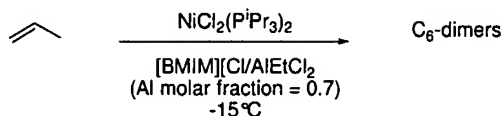
b) Knifton (1987):



c) Wilkes et al. (1990):



d) Chauvin et al. (1990):



Scheme 5.3-1 Early examples of transition metal catalysis in ionic liquids.

ionic liquids with weakly coordinating anions – the properties of relatively polar yet non-coordinating solvents. This special combination makes them extremely suitable solvents for reactions with electrophilic catalysts [8]. Moreover, these ionic liquids are now widely available commercially [9] so that research groups and companies focusing on catalytic applications do not necessarily have to go through all of the synthetic work themselves (for the synthesis of ionic liquids and especially for the quality requirements related to their applications as solvents in homogeneous catalysis see Chapter 2).

However, we have to be aware of a number of limitations when applying tetrafluoroborate and hexafluorophosphate ionic liquids as reaction media in homogeneous catalysis. The major problem is that these anions are sensitive to hydrolysis. The tendency to anion hydrolysis is of course much less pronounced than for chloroaluminate melts (the latter immediately hydrolyze completely to HCl and Al oxides when in contact with sufficient amounts of water). Anion hydrolysis of tetrafluoroborate and hexafluorophosphate ionic liquids has been shown to occur under relatively moderate conditions [10] and well within the time-scale of an ordinary catalytic experiment (over a few hours significant decomposition can be observed

1 in a wet system under slightly elevated temperatures), which makes these effects  
2 important for the correct interpretation of the results of even laboratory screen-  
3 ing experiments. The hydrolytic formation of HF from the hexafluorophosphate  
4 and tetrafluoroborate anion causes the following problems with regard to their use  
5 as solvents for transition metal catalysis: (i) loss or partial loss of the ionic liquid  
6 solvent; (ii) corrosion problems related to the HF formed; (iii) deactivation of the  
7 transition metal catalyst through its irreversible complexation by  $F^-$  ions. Conse-  
8 quently, the application of tetrafluoroborate and hexafluorophosphate ionic liquids  
9 is effectively restricted to those applications where water-free conditions can be  
10 realized at acceptable effort. This pre-condition is certainly fulfilled in cases where  
11 the transition metal complex under investigation or the substrates used are water-  
12 sensitive themselves, so that the reaction has to be carried out under inert and  
13 water-free conditions anyway.

14 In 1996, Grätzel, Bonhôte and coworkers published the synthesis and proper-  
15 ties of ionic liquids with anions containing  $CF_3$  and other fluorinated alkyl groups  
16 [11]. These do not show the same sensitivity towards hydrolysis as  $[BF_4]^-$  and  
17  $[PF_6]^-$ -containing systems. In fact, heating  $[BMIM][CF_3SO_2)_2N]$  with excess water to  
18 100 °C for 24 h did not reveal any hint of anion hydrolysis. The first success-  
19 ful catalytic experiments using these ionic liquid systems have been reported,  
20 e.g., the hydrovinilation of styrene catalyzed by a cationic nickel complex in  
21  $[EMIM][CF_3SO_2)_2N]$  [12]. However, despite the very high stability of these salts  
22 to hydrolysis and a number of other very suitable properties (e.g. low viscosity, high  
23 thermal stability, easy preparation in halogen-free form due to miscibility-gap with  
24 water) the relatively high price of  $[CF_3SO_2)_2N]^-$  and related anions may be a major  
25 problem for their practical application in larger quantities (the Li salt is commercially  
26 available from both Rhodia and 3M). Moreover, the disposal of spent ionic liquids of  
27 this type, e.g., by combustion, is more complicated due to potential HF liberation.

28 In this context, the use of ionic liquids with halogen-free anions has become  
29 more and more popular. In 1998, Andersen et al. described the use of phosphonium  
30 tosylates (all with melting points > 70 °C) in the Rh-catalyzed hydroformylation of  
31 1-hexene [13]. More recently, much lower melting imidazolium-based alkylsulfate  
32 and oligoethersulfate ionic liquids have been prepared [14] and used as solvents  
33 in transition metal catalysis [15]. For example,  $[BMIM][n-C_8H_{17}SO_4]$  (mp = 35 °C)  
34 could be used as a catalyst solvent in the rhodium catalyzed hydroformylation of  
35 1-octene. It can be anticipated that the further development of transition metal  
36 catalysis in ionic liquids will be driven to a significant extent by the availability of  
37 new ionic liquids with different anion systems. In particular, cheap, halogen-free  
38 systems that combine weak coordination to electrophilic metal centers and low  
39 viscosity with high stability to hydrolysis are highly desirable.

40 Transition metal catalysis in ionic liquids is a field of great research activity (in  
41 particular over the last five years) which has also generated an extensive review-  
42 ing practice. Latest examples originated from Welton [16], MacFarlane [17] and  
43 Pozzi [18] and compiled the development of the research field in a more or less  
44 comprehensive way, though with slightly different emphasis from their specific,  
45 different viewpoints. These four up-dated earlier published reviews by Dupont [19],



Zhao [20], Haag [21], Dobbs [22], Olivier-Bourbigou [23], Sheldon [24], Gordon [25], Wasserscheid [26], Welton [27] and Seddon [28] on the same topic.

In contrast to most of these reviews, the present section will have a clearly instructive character. It aims to derive general principles from the work published so far in order to give the reader a useful overall understanding of the achievements and remaining challenges in transition metal catalysis using ionic liquids. The chapter will be structured in two major parts. Section 5.3.1 will present general and conceptual aspects, motivations, successful strategies and limiting factors. The latter could not yet be overcome or have been found out in the meanwhile to be intrinsic to the concept of performing transition metal catalysis in ionic liquids.

In Section 5.3.2 we will review selected transition metal catalyzed reactions with the clear aim to further illustrate the principles derived in Section 5.3.1. For this selection a number of criteria were considered: (i) the general and technical relevance of the transition metal catalyzed reaction; (ii) the degree of understanding concerning the ionic liquid's role; and finally (iii) the potential to transfer key results to future, new applications. The (obviously somewhat subjective) selection includes transition metal catalyzed hydrogenation, oxidation, hydroformylation, Pd-catalyzed C–C-coupling and dimerization/oligomerization reactions as well as catalysis involving transition metal nanoparticles. Regarding these selected applications our chapter aims for a sound overview, however comprehensiveness is not guaranteed. The missing work has been left out to avoid information overload. Thus, we would like to apologize at this point for having omitted also a number of sound and important papers for the reason of improved clarity. We do appreciate very much all contributions to advance ionic liquid research with respect to transition metal catalysis!

With the dual approach of Sections 5.3.1 and 5.3.2 we would like to share our experience in particular with readers working in the field of transition metal catalysis, but so far inexperienced in using ionic liquids. Our section aims to provide some guidelines and is intended to encourage these scientists to test and develop ionic liquids as parts of a "tool box" for their future research.

### 5.3.1

#### Concepts, Successful Strategies, and Limiting Factors

##### 5.3.1.1 Why Use Ionic Liquids as Solvents for Transition Metal Catalysis?

###### *The non-volatile nature*

Probably the most prominent property of an ionic liquid is its extremely low vapor pressure [29]. Transition metal catalysis in ionic liquids can particularly benefit from this on economic, environmental and safety grounds.

Obviously, the use of a non-volatile ionic liquid simplifies the distillative work-up of volatile products, especially in comparison to the use of low boiling solvents, where this may save the distillation of the solvent during product isolation. Moreover, common problems related to the formation of azeotropic mixtures of a volatile solvent and the products/by-products formed, are avoided by using a non-volatile

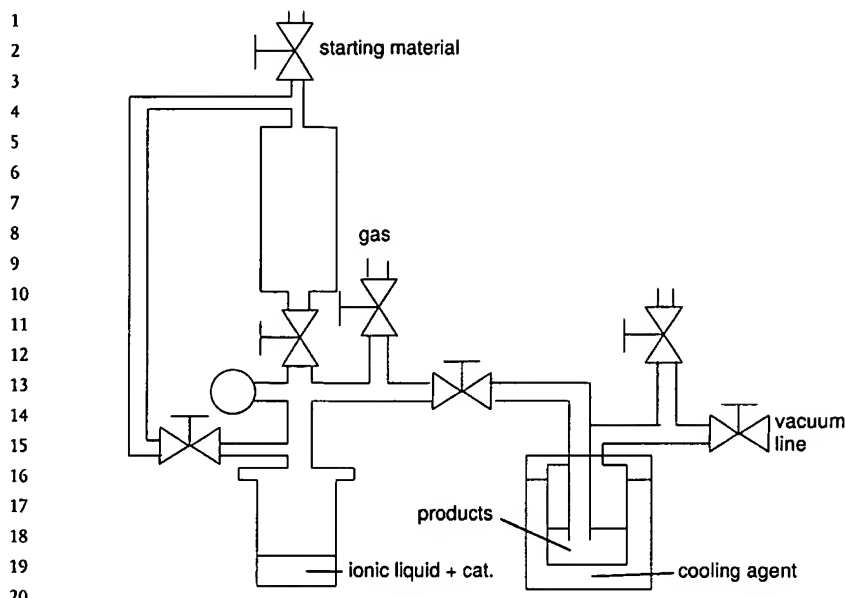


Fig. 5.3-1 Stabilization of an active rhodium catalyst by addition of the ionic liquid [BMIM][PF<sub>6</sub>] as co-solvent during distillative product isolation – apparatus for distillative product isolation from the ionic catalyst layer.

ionic liquid. In the Rh-catalyzed hydroformylation of 3-pentenoic acid methyl ester it was even found that the ionic liquid added could stabilize the homogeneous catalyst during the thermal stress of product distillation (Fig. 5.3-1) [30]. This option may be especially attractive technically, due to the fact that the stabilizing effects could already be observed with quite low amounts of ionic liquid added.

As in stoichiometric organic reactions, the application of non-volatile ionic liquids can contribute to the reduction of atmospheric pollution. This is of special relevance for non-continuous reactions where complete recovery of a volatile organic solvent is usually difficult to integrate into the process.

As well as this quite obvious environmental aspect, the switch from a volatile, flammable, organic solvent to an ionic liquid may significantly improve the safety of a given process. This is especially true for oxidation reactions where air or pure oxygen are used as oxidants. Here, the use of common organic solvents is often restricted by the potential formation of explosive mixtures between oxygen and the volatile organic solvent in the gas phase. Therefore, it is anticipated that there will be some technical applications for ionic liquids in the future where solely the advantage of their non-volatile character is used for mainly safety reasons.

Very recently, a new concept to process transition metal catalysis in ionic liquids has been introduced that makes explicit use of the extremely low volatility of ionic liquids. It comprises the immobilization of a transition metal catalyst in an ionic

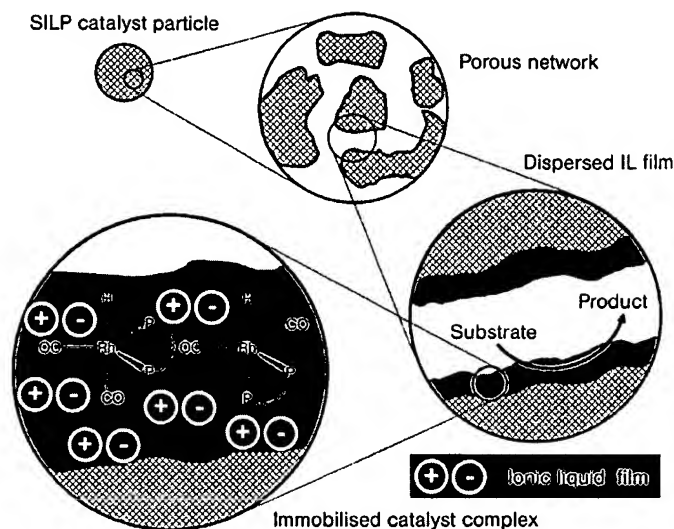


Fig. 5.3-2 Schematic representation of a supported ionic liquid phase (SILP) catalyst exemplified for a typical rhodium hydroformylation catalyst.

liquid. The resulting solution is confined on the surface of a highly porous solid by various methods such as, e.g. physisorption, tethering, or covalent anchoring of ionic liquid fragments [31]. This preparation results in a solid that contains, in a supported liquid film, a homogeneously dissolved transition metal complex. During catalytic reactions using such a supported ionic liquid phase (SILP) catalyst the feedstock molecules diffuse through the residual pore space of the catalyst, dissolve in the ionic liquid catalyst phase, and react at dissolved transition metal complexes within the thin liquid catalyst film dispersed on the walls of the pores in the support material. The products then diffuse back out of the catalyst phase into the void pore space and further out of the catalyst particle (see Fig. 5.3-2).

The reactants in SILP catalysis are preferentially processed in gaseous form. Processing of solid SILP catalysts in a liquid reaction phase as a slurry requires extremely low solubility of the ionic liquid film in the liquid reaction mixture and affords special constraints upon the mechanical stability of the liquid film. In contrast, for the – by far more attractive – gas-phase applications of SILP catalysts the extremely low volatility of the ionic liquids is the key success factor. It is noteworthy that earlier attempts to apply supported liquid catalysts in continuous gas phase reactions – using organic liquid phases [32] or water [33] as the immobilized liquid phase – resulted in catalyst systems too unstable for technical use due to evaporation of the liquid film with time. In contrast, SILP systems have been shown to be stable in activity and selectivity for several hundreds hours on stream [34]. The excellent performance of SILP catalysts has been demonstrated for hydroformylations [35] (Rh-catalyzed), hydrogenation [36] (Rh-catalyzed), Heck reactions

## 374 | 5 Organic Synthesis

[37] (Pd-catalyzed), hydroaminations [38] (Rh-, Pd- and Zn-catalyzed) and methanol carbonylation [39] (Rh-catalyzed). The concept of using a supported ionic liquid catalyst combines the most attractive features of homogeneous catalysis (such as high specificity and dispersion of the catalyst) with the most attractive features of heterogeneous catalysts (such as large interfacial reaction area and ease of separation of the products from the catalyst). Finally, SILP catalysts allow the application of conventional fixed-bed reactor process technology for homogeneous catalysis. Combined, these features have made the methodology very attractive for future technical applications (for more details about SILP catalysis see Section 5.6).

**New opportunities for biphasic catalysis**

In comparison to heterogeneous catalyzed reactions, homogeneous catalysis offers several important advantages. The catalyst complex is usually well defined and can be rationally optimized by ligand modification. Every metal center can be active in the reaction. The reaction conditions are usually much milder ( $T$  usually  $<200\text{ }^{\circ}\text{C}$ ) and selectivities are often much higher than with heterogeneous catalysts.

Notwithstanding these advantages, the proportion of homogeneous catalyzed reactions in industrial chemistry is still quite low. The main reason for this is the difficulty in separating the homogeneously dissolved catalyst from the products and by-products after the reaction. Since the transition metal complexes used in homogeneous catalysis are usually quite expensive, complete catalyst recovery is crucial in a commercial situation.

Biphasic catalysis in a liquid–liquid system is another powerful approach to combine the advantages of both homogeneous and heterogeneous catalysis. The reaction mixture consists of two immiscible solvents. Only one phase contains the catalyst, allowing easy product separation by simple decantation. The catalyst phase can be recycled without any further treatment. However, the right combination of catalyst, catalyst solvent and product is crucial for the success of biphasic catalysis [40]. The catalyst solvent has to provide excellent solubility for the catalyst complex without competing with the substrate for the free coordination sites at the catalytic center.

Even more attractive is the possibility of optimizing the reaction's activity and selectivity by means of a biphasic reaction mode. This can be realized by *in situ* extraction of catalyst poisons or reaction intermediates from the catalytic layer. However, to benefit from this potential, even more stringent requirements have to be fulfilled by the catalyst solvent since the latter has to provide a specific, very low solubility for the substances that are to be extracted from the catalyst phase under the reaction conditions. Figure 5.3-3 demonstrates this concept, exemplified for an oligomerization reaction. The dimer selectivity of the oligomerization of compound A can be enhanced significantly if the reaction is carried out in biphasic mode using a catalyst solvent with high preferential solubility for A. The A–A formed is then readily extracted from the catalyst phase into the product layer, which reduces the chance for the formation of higher oligomers A–A–A and A–A–A–A.

Keeping all these circumstances in mind, it becomes understandable why the use of traditional solvents for biphasic catalysis (e.g., water or butanediol) has only been

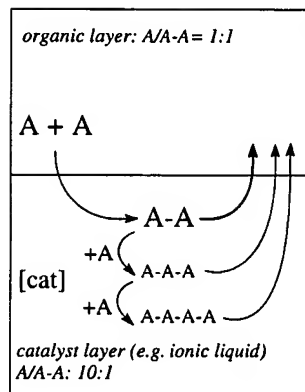


Fig. 5.3-3 Enhanced dimer selectivity in the oligomerization of compound A due to a biphasic reaction mode with a catalyst solvent of high preferential solubility for A.

able to fulfill this potential in a few specific examples [41]. Whereas, this type of highly specialized liquid–liquid biphasic operation is an ideal field for the application of ionic liquids, mainly due to their exactly tuneable physicochemical properties (see Section 3.3 for more details). Very recently it has been demonstrated that the solubility and miscibility properties of ionic liquids can be varied so widely that even mutually immiscible ionic liquids can be realized [42]. However, applications of these ionic liquid–ionic liquid biphasic systems in catalysis have not yet been described.

Reviewing the so far published literature about transition metal catalysis in ionic liquids it becomes quite clear that by far the greatest part of the work has been carried out in the form of liquid–liquid biphasic catalysis. There are three convincing arguments for the choice of this reaction mode.

- 1 In this way the catalyst complex immobilized in the ionic liquid can be easily recycled.
- 2 Liquid–liquid biphasic catalysis is a very efficient way to reuse the relatively expensive ionic liquid itself. Thus – for a commercial application – the ionic liquid may be seen as an investment for the process (in an ideal case) or at least as a “working solution”, which means that only a small amount has to be replaced after a certain time of application. In fact, for any kind of recycling process the ionic catalyst solution (transition metal complex + ionic liquid) has to be regarded as an entity. With regards to this aspect liquid–liquid biphasic catalysis with ionic liquids is better regarded as a kind of heterogeneous catalysis using a liquid, non-volatile support material which is a fundamentally different approach compared to conventional homogeneous catalysis in an organic solvent.
- 3 Most catalytic applications using ionic liquids aim to realize beneficial effects with the lowest possible amount of ionic liquid present in the system. A fully

soluble ionic liquid would thus lead to the situation where a very small amount of ionic liquid would be dissolved in a large volume of reaction mixture. In such a scenario the ions of the ionic liquid would be present as either fully dissociated and solvated cations/anions or as solvated ion-pairs depending on the polarity of the reactants. But can this still be regarded as being an ionic liquid? In contrast, an immiscible ionic catalyst solution retains its specific ionic liquid character even if the immiscible, organic reactant/product phase is used in large volumetric excess.

Due to the great importance of liquid–liquid biphasic catalysis for ionic liquids, Section 5.4 will be dedicated to specific aspects related to this mode of reaction, with special emphasis on practical, technical and engineering needs. Section 5.7 will summarize a very interesting recent development for biphasic catalysis with ionic liquids, namely the use of ionic liquid–compressed CO<sub>2</sub> biphasic mixtures in transition metal catalysis.

#### ***Activation of a transition metal catalyst in ionic liquids***

Apart from the activation of a biphasic reaction by extraction of catalyst poisons, described above, the ionic liquid solvent can activate homogeneously dissolved transition metal complexes by chemical interaction.

In general, it is possible for a chemical interaction between the ionic liquid solvent and a dissolved transition metal complex to be either activating or deactivating. Therefore, understanding these chemical interactions is crucial to benefit from this potential and to avoid deactivation. Everything is traced back to the rather obvious question of how much the presence of a specific ionic liquid influences the electronic and steric properties of the active catalyst complex and – perhaps even more importantly – to what extent the ionic liquid influences the availability of free coordination sites at the catalytic center for the substrates that are supposed to undergo the catalysis. Clearly, an exact knowledge of both the catalytic mechanism in common organic solvents and the chemical properties of the ionic liquid is very helpful in understanding these different effects.

In the following section, the nature of chemical interactions between an ionic liquid and a transition metal catalyst is systematically developed according to the role of the ionic liquid in the different systems.

##### **5.3.1.2 The Role of the Ionic Liquid**

Depending on the coordinative properties of the anion and on the degree of the cation's reactivity, the ionic liquid can be regarded as “innocent” solvent, as ligand (or ligand precursor), as co-catalyst or as the catalyst itself.

#### ***The ionic liquid as “innocent” solvent***

Ionic liquids with weakly coordinating, inert anions (e.g., [(CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>N]<sup>−</sup>, [BF<sub>4</sub>]<sup>−</sup>, [SbF<sub>6</sub>]<sup>−</sup> or [PF<sub>6</sub>]<sup>−</sup> under anhydrous conditions) and inert cations (cations that do not coordinate to the catalyst themselves and that do not form species under the

1 reaction conditions that coordinate to the catalyst) can be considered as more or less  
2 “innocent” solvents in transition metal catalysis. In these cases, the role of the ionic  
3 liquid is to provide a more or less polar, more or less weakly coordinating medium  
4 for the transition metal catalyst that additionally offers special solubility properties  
5 for feedstock and products.

6 However, the chemical inertness of these “innocent” ionic liquids does not mean  
7 that the reactivity of a transition metal catalyst dissolved in the ionic liquid is nec-  
8 essarily equal to the reactivity observed in common organic solvents. This becomes  
9 understandable from the fact that many organic solvents are applied in catalytic  
10 reactions that do not behave as innocent solvents, but show significant coordina-  
11 tion to the catalytic center. The reason why these solvents are nevertheless used in  
12 catalysis is that some polar or ionic catalyst complexes are not soluble enough in  
13 weakly coordinating organic solvents. For example, many cationic transition metal  
14 complexes are known to be excellent oligomerization catalysts [43]. However, their  
15 usually poor solubility in non-polar solvents often requires a compromise between  
16 the solvation and the coordination properties of the solvent, if organic solvents  
17 are used. In order to achieve sufficient solubility of the metal complex a solvent  
18 of higher polarity is required, that may compete with the substrate for the coor-  
19 dination sites at the catalytic center. Consequently, in these cases, the use of an  
20 inert, weakly coordinating ionic liquid (such as a hexafluorophosphate ionic liq-  
21 uid) can result in a clear enhancement of catalytic activity, since these ionic liquids  
22 are known to combine high solvation power for polar catalyst complexes (polar-  
23 ity) with weak coordination (nucleophilicity) [44]. It is this combination of prop-  
24 erties of the ionic liquids that cannot be realized with water or common organic  
25 solvents.

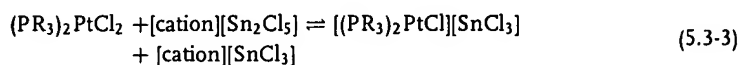
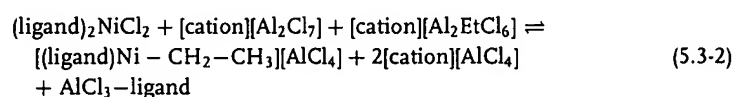
26 Despite the great potential of these “weakly coordinating” ionic liquids in com-  
27 bination with highly electrophilic, polar or ionic catalyst complexes, it should be  
28 noted that the anions of an ionic liquid are more likely to coordinate to the metal  
29 center of a dissolved complex than the same anions dissolved in a molecular solvent  
30 would do [16]. This point becomes understandable considering a cationic metal  
31 center (coordinatively unsaturated with vacant orbitals) dissolved in a molecular  
32 solvent. The possibilities are (i) an anion can directly coordinate to the metal center,  
33 (ii) the anion and the cation may be well separated in the solvent, with the cation  
34 coordinated to molecules of the solvent, or the cation and anion can exist as either  
35 (iii) an intimate, or (iv) a solvent separated ion-pair. In a pure ionic liquid there are  
36 no molecules available to separate the ions and the cations of the ionic liquid will  
37 be repelled by the charge on the metal complex. Hence, only options (i) and (iii) are  
38 available. Thus the cationic center will always be closely associated with the anions  
39 of the ionic liquid and this interaction will greatly determine its reactivity.

#### 42 *Ionic liquid as solvent and co-catalyst*

43 Ionic liquids formed by the reaction of a halide salt with a Lewis acid (e.g. chloroa-  
44 luminate or chlorostannate melts) generally act as both solvent and co-catalyst in  
45 transition metal catalysis. The reason for this is that the Lewis acidity or basicity,

## 378 | 5 Organic Synthesis

which is always present (at least latently), results in strong interactions with the catalyst complex. In some cases, the Lewis acidity of an ionic liquid is used to convert the neutral catalyst precursor into the corresponding cationic, catalytically active form. The activation of  $\text{Cp}_2\text{TiCl}_2$  [45] and  $(\text{ligand})_2\text{NiCl}_2$  [46] in acidic chloroaluminate melts and the activation of  $(\text{PR}_3)_2\text{PtCl}_2$  in chlorostannate melts [47] are examples of this kind of activation [Eqs. (5.3-1)–(5.3-3)].



In those cases where the ionic liquid is not directly involved in creating the active catalytic species, a co-catalytic interaction between the ionic liquid solvent and the dissolved transition metal complex may still take place and can result in significant catalyst activation. When a catalyst complex is, for example, dissolved in a slightly acidic ionic liquid some electron-rich parts of the complex (e.g., lone pairs of electrons in the ligand) will interact with the ionic liquid in a way that will usually result in a lower electron density at the catalytic center. If this higher electrophilicity of the catalytic center results in a higher catalytic activity (e.g., as in oligomerization reactions of most olefins) then there is a very good chance of activating the catalyst system in a slightly acidic ionic liquid. In fact, this is the reason why many Ni-catalyzed oligomerization reactions of propene and butene have been carried out very successfully in slightly acidic or buffered chloroaluminate ionic liquids (see Section 5.3.2.5 for more details). It is noteworthy, that this type of co-catalytic influence is well-known in heterogeneous catalysis where, for some reactions, an acidic support activates the dispersed metal catalyst better than do neutral supports. Such comparison justifies regarding acidic ionic liquids in transition metal catalysis as a kind of liquid acidic support for the metal complex dissolved therein.

As one would expect, in those cases where the ionic liquid acts as a co-catalyst, the nature of the ionic liquid becomes very important for the reactivity of the transition metal complex. The chance to optimize the ionic reaction medium by variation of the halide salt, the Lewis acid and the ratio of the two components forming the ionic liquid, opens up enormous potential for optimization. However, the choice of these parameters may be restricted by some possible incompatibilities with the feedstock used. Undesired side reactions caused by the Lewis acidity of the ionic liquid or strong interaction between the Lewis acidic ionic liquid and, for example, some oxygen functionalities in the substrate have to be considered.

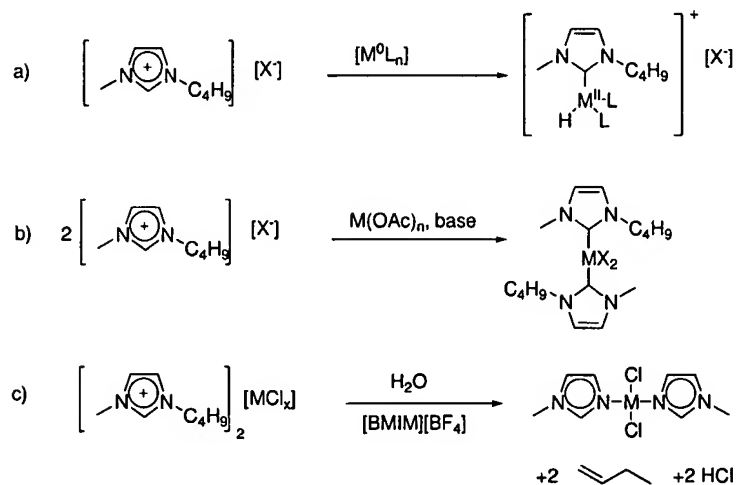


**Ionic liquid as solvent and ligand/ligand precursor**

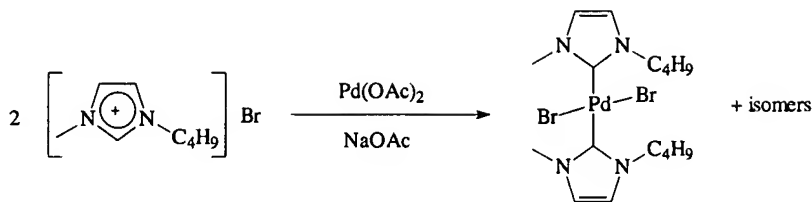
Both cation and anion of an ionic liquid can act as a ligand or ligand precursor for a transition metal complex dissolved in the ionic liquid.

Anions of the ionic liquid may act, to some degree, as ligands if the catalytic center is cationic, depending on their coordination strength. Indeed, it has been clearly demonstrated that the anion of a cationic transition metal complex is replaced to a large extent by the ionic liquid's anion if they are different [12]. While most of the ionic liquid anions used in catalysis are chosen to interact as weakly as possible with the catalytic center, this situation may change dramatically if the ionic liquid's anion undergoes decomposition reactions. If the hexafluorophosphate anion of an ionic liquid hydrolyses in contact with water, for example, strongly coordinating fluoride ions are liberated that will act as strong ligand and catalyst poison to many transition metal complexes.

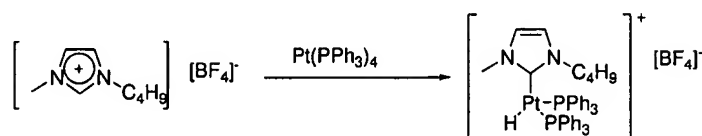
With respect to the ionic liquid's cation the situation is quite different, since catalytic reactions with anionic transition metal complexes are not yet very common in ionic liquids. However, the 1,3-dialkylimidazolium cation can act as a ligand precursor for the dissolved transition metal. Its transformation under the reaction conditions into a ligand has been observed in three different ways: (i) formation of metal carbene complexes by oxidative addition of the imidazolium cation; (ii) formation of metal-carbene complexes by deprotonation followed by coordination of the imidazolylidene on the metal center; (iii) dealkylation of the imidazolium cation and formation of a metal imidazole complex. These different ways are displayed in a general form in Scheme 5.3-2.



**Scheme 5.3-2** Different routes for an *in situ* ligand formation from the ionic liquid's 1,3-dialkylimidazolium cation.



**Scheme 5.3-3** Formation of a Pd-carbene complex by deprotonation of the imidazolium cation.



**Scheme 5.3-4** Formation of a Pt-carbene complex by oxidative addition of the imidazolium cation.

The second reaction pathway ((b) in Scheme 5.3-2) is based on the well-known, relatively high acidity of the H atom in the 2-position of an 1,3-dialkylimidazolium ion [48]. The latter can be deprotonated (e.g. by basic ligands of the metal complex or by basic reactants) to form a metal-carbene complex. Xiao and coworkers demonstrated that a Pd imidazolylidene complex is formed when Pd(OAc)<sub>2</sub> was heated in the presence of [BMIM]Br [49]. The isolated Pd-carbene complex was found to be active and stable in Heck coupling reactions (for more details see Section 5.3.2.4). Welton et al. were later able to characterize an isolated Pd-carbene complex obtained in this way by X-ray spectroscopy [50]. The reaction pathway to form the complex is displayed in Scheme 5.3-3.

However, the formation of the metal-carbene complex was not observed in pure, halide-free [BMIM][BF<sub>4</sub>], indicating that the formation of carbene depends on the nucleophilicity of the ionic liquid's anion. To avoid the formation of metal-carbene complexes by deprotonation of the imidazolium cation under basic conditions the use of 2-methyl-substituted imidazolium is frequently suggested. However, it should be mentioned here that strong bases can also abstract a proton to form the vinyl imidazolidene species which may also act as a strong ligand to electrophilic metal centers.

Another method of *in situ* metal-carbene complex formation in an ionic liquid is the direct oxidative addition of the imidazolium cation on a metal center in a low oxidation state (see Scheme 5.3-2(a)). Cavell and coworkers have observed oxidative addition by heating 1,3-dimethylimidazolium tetrafluoroborate with Pt(PPh<sub>3</sub>)<sub>4</sub> in refluxing THF [51]. The Pt-carbene complex formed can decompose by reductive elimination. Winterton et al. have also described the formation of a Pt-carbene complex by oxidative addition of the [EMIM]<sup>+</sup> cation to PtCl<sub>2</sub> in a basic [EMIM]Cl/AlCl<sub>3</sub> (free Cl<sup>-</sup> ions present) under ethylene pressure [52]. The formation of a Pt-carbene complex by oxidative addition of the imidazolium cation is displayed in Scheme 5.3-4.

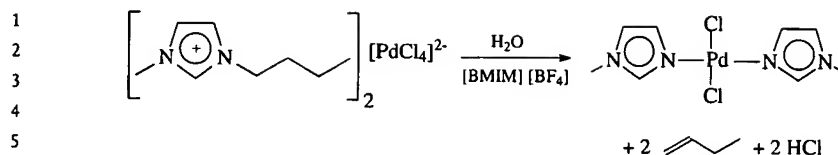
1 Not only platinum forms carbene complexes by oxidative addition of 1,3-  
2 dialkylimidazolium salts. Cavell and coworkers also reported the formation of stable  
3 carbene complexes of nickel and palladium by reaction with imidazolium ionic liq-  
4 uids [53]. Even in cases where the imidazolium was protected with a methyl group  
5 in the 2-position of the imidazolium ring, carbene formation has been observed in  
6 the 4- or 5-position in some cases [54].

7 In the light of these results, it becomes important to question whether a particular  
8 catalytic result obtained in a transition metal catalyzed reaction in an imidazolium  
9 ionic liquid is in fact caused by a metal–carbene complex formed *in situ*. The follow-  
10 ing simple experiments can help to check this point out in more detail: (i) variation  
11 of ligands in the catalytic system; (ii) application of independently prepared, defined  
12 metal–carbene complexes; (iii) investigation of the reaction in pyridinium, tetraalky-  
13 lammonium, tetraalkylphosphonium or 1,2,3-trialkylimidazolium-based ionic liq-  
14 uids. If the reaction shows significant sensitivity to the use of different ligands,  
15 if the application of the independently prepared, defined metal–carbene complex  
16 shows a different reactivity than the catalytic system under investigation or if the  
17 catalytic result in the ionic liquid with non-carbene-forming cations is similar to the  
18 catalytic result in the 1,3-dialkylimidazolium system, then a significant influence of  
19 a metal–carbene complex formed *in situ* is unlikely. Of course, even then, the *in situ*  
20 formation of a metal–carbene complex cannot be totally excluded, but its lifetime  
21 may be very short so that there is not a significant influence on the catalysis.

22 It is interesting to note that the *in situ* formation of transition metal–carbene  
23 complexes has been used to explain both increased catalyst activity and stability as  
24 well as catalyst instability and deactivation. While Basset and coworkers attributed  
25 the complete deactivation of their Pd catalyst for the telomerization of butadiene and  
26 methanol in 1,3-dialkylimidazolium ionic liquids to the formation of highly stable  
27 Pd-imidazolylidene from palladium(II) acetate [55], Welton and coworkers ascribed  
28 the high activity of their Pd catalyst in the Suzuki cross-coupling reaction to the *in*  
29 *situ* formation of a mixed phosphine/imidazolylidene complex [56]. Both authors  
30 may well be right with their respective interpretations. The key to understanding the  
31 different behavior is probably the question of whether the ionic liquid as the source  
32 of the ligand (which as the solvent is naturally in very large excess vs. the metal  
33 complex) still allows the formation of free coordination sites at the active catalytic  
34 center. One can speculate that in a mixed phosphine/imidazolylidene system the  
35 phosphine ligand sterically prevents complete “carbene saturation” of the palladium  
36 center while in the telomerization system the butadiene substrate cannot compete  
37 with the carbene ligands for the coordination sites.

38 Finally, a third way of ligand formation from a 1,3-dialkylimidazolium cation  
39 has been described by Dupont and coworkers [57]. They investigated the hy-  
40 drodimerization/telomerization of 1,3-butadiene with palladium(II) compounds  
41 in [BMIM][BF<sub>4</sub>]. They describe the activation of the catalyst precursor complex  
42 [BMIM]<sub>2</sub>[PdCl<sub>4</sub>] via a palladium(IV) compound, which is formed by oxidative  
43 addition of the imidazolium with cleavage of the C–N bond of the [BMIM]<sup>+</sup> ion  
44 leading to dichloro-bis(methylimidazole)-palladium (Scheme 5.3-5). However, this  
45 reaction was only observed in the presence of water.

## 382 | 5 Organic Synthesis



**Scheme 5.3-5** Formation of the active Pd catalyst from [BMIM]<sub>2</sub>[PdCl<sub>4</sub>] for the hydrodimerization of 1,3-butadiene.

### 10 Ionic liquid as solvent and transition metal catalyst

11 Acidic chloroaluminate ionic liquids have already been described in Section 5.2  
 12 as both solvents and catalysts for reactions conventionally catalyzed by AlCl<sub>3</sub>, e.g.  
 13 catalytic Friedel-Crafts alkylation [58] or stoichiometric Friedel-Crafts acylation  
 14 [59]. Similarly, Lewis-acidic transition metal complexes can form complex anions  
 15 by reaction with organic halide salts. Seddon and coworkers patented, for example,  
 16 a Friedel-Crafts acylation process based on an acidic chloroferrate ionic liquid  
 17 catalyst [60].

18 However, ionic liquids acting as transition metal catalysts are not necessarily  
 19 based on classical Lewis acids. Dyson et al. published, for example, the ionic liquid  
 20 [BMIM][Co(CO)<sub>4</sub>] [61]. The system was obtained as an intense blue–green colored  
 21 liquid by metathesis reaction of [BMIM]Cl and Na[Co(CO)<sub>4</sub>]. The liquid was used as  
 22 a catalyst in the debromination of 2-bromoketones to their corresponding ketones.  
 23 An ionic liquid with the complex rhodium-carbonyl anion [Rh(CO)<sub>2</sub>I<sub>2</sub>]<sup>–</sup> was later  
 24 published by the same authors [62].

25 Examples in which the cation of the ionic liquid contains the transition metal  
 26 complex for catalysis have also been published. For example, Forbes and coworkers  
 27 [63] synthesized a Rh-containing ionic liquid cation by replacing an acetate ligand  
 28 at the Rh center by a carboxylic acid functionalized imidazolium moiety. The mod-  
 29 ified dirhodium(II) dimer of this kind was applied as an effective catalyst in the  
 30 intermolecular cyclopropanation reaction of styrene using ethyl diazoacetate.

31 In general, the incorporation of the active transition metal catalyst into the cation  
 32 or anion of an ionic liquid appears to be an attractive concept for applications where  
 33 a high catalyst concentration is needed. However, the physicochemical properties  
 34 (in particular melting point and viscosity) of such ionic liquids may be unfavorable  
 35 in many cases if such an ionic liquid is used in neat form.

#### 37 5.3.1.3 Methods for Analysis of Transition Metal Catalysts in Ionic Liquids

38 Earlier in this section we stated that in many respects transition metal catalysis  
 39 in ionic liquids is better regarded as heterogeneous catalysis on a liquid support  
 40 than as conventional homogeneous catalysis in an alternative solvent. As in  
 41 heterogeneous catalysis, support–catalyst interactions are known in ionic liquids  
 42 and can lead to catalyst activation (see Section 5.3.1.2 for more details). Product  
 43 separation from an ionic catalyst layer is often easy (at least if the products are  
 44 not too polar and have a significant vapor pressure) as in classical heterogeneous  
 45 catalysis. However, mass transfer limitation problems (when the chemical kinetics

are fast) and some uncertainty concerning the exact micro-environment around the catalytically active center represent common characteristics for transition metal catalysis in ionic liquids and in heterogeneous catalysis.

However, despite all these similarities we should not forget that it is possible to optimize the catalytically active center in ionic liquids by molecular synthesis and ligand design, which is of course much easier and more efficient than to synthesize highly defined solid surfaces. Another very important difference – that should in particular be treated in this sub-section – is the possibility to analyze the active catalyst in an ionic liquid in a much easier and often more insightful way than this is possible for the surfaces of heterogeneous catalysts. In principle, this important advantage should enable more rational catalyst development and thus much quicker catalyst optimization times.

Unfortunately, most attempts to characterize catalytically active transition metal complexes in ionic liquids have been based on product analysis. There is nothing wrong with the argument that a catalyst is more active because it produces more of the product. However, this is not the type of explanation that can help to develop a more general understanding of what happens to a transition metal complex under catalytic conditions in a certain ionic liquid.

Applying spectroscopic methods to the analysis of active catalysts in ionic liquids is not an easy task. Three aspects illustrate this: (i) As for catalysis in conventional media, the lifetime of the catalytically active species will be very short, which makes it difficult to observe. (ii) In a realistic catalytic scenario the concentration of the catalyst in the ionic liquid will be very low. (iii) The presence and concentration of the substrate will influence the catalyst/ionic liquid interaction. These three aspects alone clearly show that an ionic liquid/substrate/catalyst system is quite complex and may not be easy to study by spectroscopic methods.

In the eighties and early nineties a great deal of effort was made to study transition metal complexes in chloroaluminate ionic liquids (see Section 6.1 for some examples). The investigations at this time generally started with electrochemical studies [64] but included also spectroscopic and complex chemistry experiments [65]. With the development of the first catalytic reactions in ionic liquids, the general research focus turned away from the basic studies of metal complexes dissolved in ionic liquids. Nevertheless, the relatively small number of papers published in the last few years that deal with spectroscopic investigations of transition metal catalysis in ionic liquids clearly demonstrate the value of this kind of analytic work for the overall development of this field.

To underline this point, we aim to present in the following sub-sections a few examples of such successful analytic approaches structured by the different methodologies that were used.

#### **NMR spectroscopy**

NMR spectroscopy is a routine method in all synthetic laboratories. *In situ* NMR spectroscopy is, therefore, a natural first choice when it comes to the characterization of catalysts dissolved in ionic liquids. However, this method suffers in particular

1 from the low concentration of the catalyst in the ionic liquid. Moreover,  $^1\text{H}$ - and  
2  $^{13}\text{C}$ -NMR spectroscopic investigations are difficult, since the intense signals of the  
3 ionic liquid often make a clear detection of the dissolved catalyst difficult.

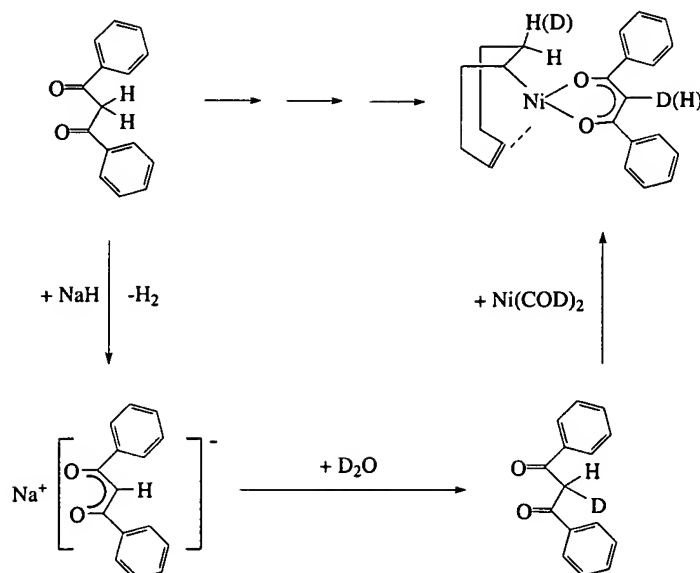
4 Several papers have been published on improving the sensitivity of NMR spec-  
5 troscopy with regard to the detection of solutes in ionic liquids. Giernoth's group  
6 suggested to use the fluorine nuclei of anions like  $[\text{BF}_4]^-$  or  $[(\text{CF}_3\text{SO}_2)_2\text{N}]^-$  as  
7 an internal  $^{19}\text{F}$  lock signal rather than to lock via the deuterium channel using a  
8 coaxial tube insert, as the latter practice makes the lock level often a bad indica-  
9 tor for the shim quality [66]. Hardacre and coworkers described the synthesis and  
10 application of fully deuterated ionic liquids [67]. An alternative, transition-metal  
11 free ring deuteration of imidazolium ionic liquid cations was recently presented  
12 by Giernoth [68]. The same author also reported a remarkable method to separate  
13 ionic liquid signals from reactant (and potentially also catalyst) signals by mak-  
14 ing use of the different mobilities of these species in a gradient NMR experiment  
15 [69].

16 Deuteration of the ionic liquid's cation has not only been applied to obtain proton-  
17 free ionic liquids for  $^1\text{H}$ -NMR experiments but also as direct probe for the reactivity  
18 of 1,3-dialkylimidazolium based ionic liquids vs. Ir(0) nanoclusters [70]. After addi-  
19 tion of  $\text{D}_2$  to  $[\text{BMIM}][(\text{CF}_3\text{SO}_2)_2\text{N}]$  in the presence of an Ir(0) nanocluster Finke and  
20 coworkers found deuterium incorporation at the 2-H, 4-H, 5-H and 8-H positions  
21 of the imidazolium cation while the control experiment in the absence of the Ir(0)  
22 cluster showed no D-incorporation. The authors concluded from their  $^2\text{H}$ -NMR ex-  
23 periments that a sequence of N-heterocyclic carbene formation by oxidative addition  
24 (see Section 3.1.2 for more details) of the imidazolium cation, H/D scrambling  
25 atop the nanocluster surface, followed by the reductive elimination of a C-D bond  
26 takes place. From careful kinetic investigations the authors concluded that the co-  
27 ordinatively unsaturated nanocluster surface acts indeed as the true catalyst for the  
28 H/D-exchange reaction.

29 An example of using deuterated reactants for detailed kinetic studies of tran-  
30 sition metal catalyzed reactions in ionic liquids was contributed by Abu-Omar  
31 and coworkers. They studied the Rh-catalyzed epoxidation of olefins at ambient  
32 temperatures using  $[\text{D}_8]$ styrene and  $[\text{D}_{10}]$ -cyclohexene [71]. They also applied  $^2\text{H}$ -  
33 NMR experiments of  $[\text{D}_3]$ -diperoxorhenium, formed *in situ* by reaction of  $[\text{D}_3]$ -  
34 methyltrioxorhenium and urea hydrogen peroxide (UHP) to determine rate con-  
35 stants in single turnover experiments.

36 An example of the selective introduction of a deuterium probe into the ligand  
37 of a transition metal catalyst (followed by *in situ*  $^2\text{H}$ -NMR spectroscopy) was earlier  
38 applied to explain the activation of the square planar Ni-complex ( $\eta$ -4-cycloocten-  
39 1-yl)(1,5-diphenyl-2,4-pentandionato-O,O')nickel in slightly acidic chloroaluminate  
40 ionic liquids [72]. The D-labeled ligand was prepared according to Scheme 5.3-6  
41 by reacting 1,5-diphenyl-2,4-pentadione with NaH followed by hydrolysis with  
42  $\text{D}_2\text{O}$ . The deuterated ligand was dried and reacted with dicyclocoadienyl nickel  
43  $[\text{Ni}(\text{COD})_2]$ .

44 The  $^2\text{H}$ -NMR spectra of the deuterated complex obtained in  $\text{CH}_2\text{Cl}_2$  and in  
45  $[\text{BMIM}]\text{Cl}-\text{AlCl}_3$  (1:1.2) are displayed in Fig. 5.3-4.



**Scheme 5.3-6** Synthesis of a deuterated analogue of the square planar Ni-complex ( $\eta^4$ -cycloocten-1-yl)(1,5-diphenyl-2,4-pentandionato-O,O') nickel for  $^2\text{H}$ -NMR investigations.

While the deuterated complex shows the expected NMR signals in  $\text{CH}_2\text{Cl}_2$  (two signals from the complex and one signal from the solvent), the  $^2\text{H}$ -NMR spectrum obtained from the complex in the slightly acidic chloroaluminate ionic liquid shows only one signal indicating that the abstraction of COD is more efficient in the ionic liquid medium. Moreover, the deuterium signal of the acac ligand undergoes a significant downfield shift, suggesting intense electronic interaction between the ligand and the Lewis acidic centers of the melt. These interactions, which should result in an increased electrophilicity of the Ni-center, help to explain the activation of Ni-acac complexes in slightly acidic chloroaluminate ionic liquids.

An alternative way to gain insight into the interactions between the catalyst complex and the ionic liquid is to record changes in the ionic liquid during the addition of the catalyst complex in an indirect manner. This method has been successfully applied by van Eldik and coworkers to understand in more detail the activation of  $[(\text{PPh}_3)_2\text{PtCl}_2]$  in chlorostannate ionic liquids [73]. The authors determined the  $^{119}\text{Sn}$  NMR chemical shift of many different melt compositions  $[\text{BMIM}]\text{Cl}/\text{SnCl}_2$  and found evidence for the formation of  $[\text{Sn}_2\text{Cl}_5]^-$  anions in the acidic regime of the composition range that plays a major role in the catalyst activation. The change in color from yellow to red during the dissolution of the complex in the ionic liquid could be attributed to the insertion of  $\text{SnCl}_2$  from the dimeric anion into the Pt-Cl bond.

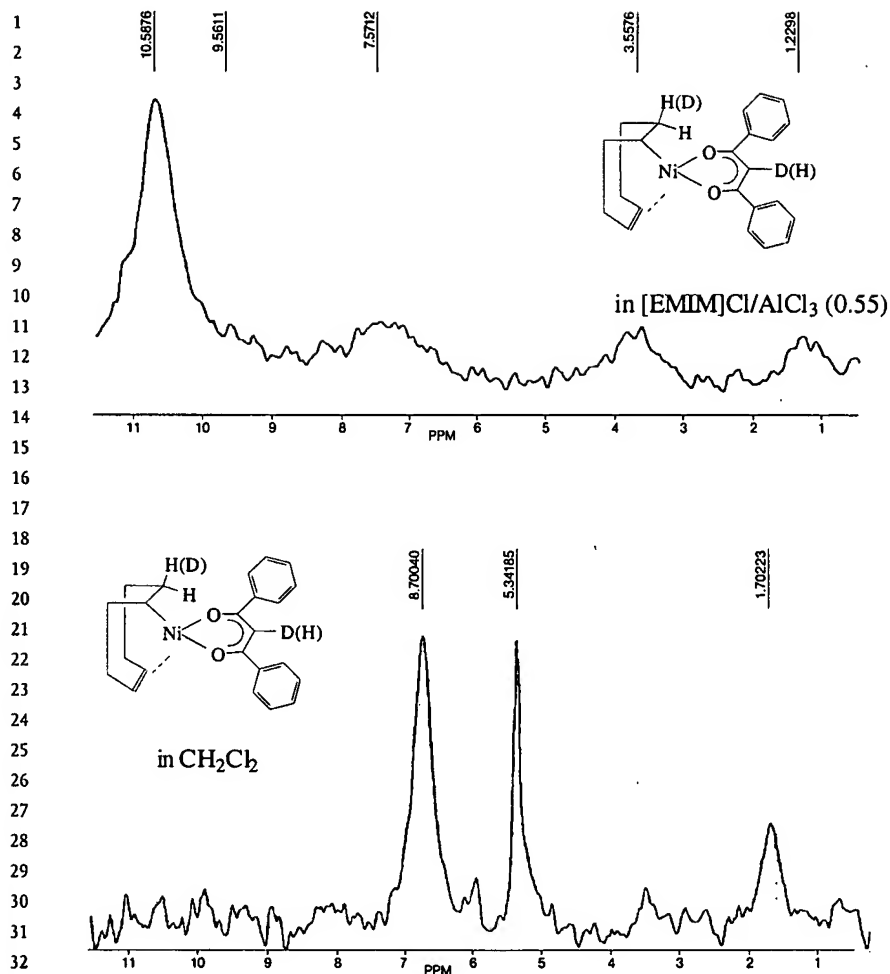


Fig. 5.3-4  $^2\text{H}$ -NMR spectra of the deuterated analogue of the square planar Ni-complex  $(\eta\text{-}4\text{-cycloocten-1-yl})$   $(1,5\text{-diphenyl-}2,4\text{-pentandionato-O,O'})$ nickel recorded in  $\text{CH}_2\text{Cl}_2$  and in  $[\text{EMIM}]\text{Cl}/\text{AlCl}_3$   $[X(\text{AlCl}_3) = 0.55]$ .

#### UV-Vis spectroscopy

The same authors also studied the kinetics of  $[(\text{PPh}_3)_2\text{PtCl}_2]$  activation in chlorostannate ionic liquids also by UV-Vis spectroscopy [73]. Apart from investigations in neat chlorostannate melt they also investigated the activation in  $[\text{BMIM}][(\text{CF}_3\text{SO}_2)_2\text{N}]$  after addition of  $[\text{BMIM}]\text{Cl}/\text{SnCl}_2$  (equimolar composition in tenfold excess to the added  $\text{Pt(II)}$ -complex). The observed reaction was found



1 to proceed in two steps, the first step could be identified as the nucleophilic  
2 substitution of  $\text{Cl}^-$  by  $[\text{SnCl}_3]^-$  which is the only anion present in this system.

3 Later van Eldik and coworkers applied UV-Vis spectroscopy to monitor  
4 the kinetics of ligand substitution reactions at the complex cation  $[\text{Pt}(\text{II})(2,6\text{-bis(aminomethyl)pyridine})\text{Cl}]^+$  using thiourea and iodide as nucleophiles [74]. They  
5 compared the reactions in water, methanol and  $[\text{BMIM}][(\text{CF}_3\text{SO}_2)_2\text{N}]$  and concluded  
6 that with respect to spectral changes, kinetic traces, rate and activation parameters  
7 the selected ionic liquid behaves as a "normal", innocent solvent in the ligand sub-  
8 stitution reactions under investigation. For the first time the authors reported an  
9 activation volume for a ligand substitution reaction in an ionic liquid and correlated  
10 this with intrinsic volume changes that result from changes in bond length and  
11 bond angles on going to the transition state of the ligand exchange reaction.

12 An example of monitoring non-steady state kinetics in ionic liquids using UV-Vis  
13 spectroscopy was published by Abu-Omar and coworkers [71]. They monitored the  
14 methyltrioxorhenium(MTO)-catalyzed olefin epoxidation in  $[\text{EMIM}][\text{BF}_4]$  by observ-  
15 ing the spectral changes of the Re complexes in the ionic liquid. The decreasing  
16 absorbance at 360 nm was attributed to the reactions of both the diperoxorhenium  
17 and the monoperoxorhenium complex with the olefinic substrate.

18 It is noteworthy that the study of transition metal catalysts in ionic liquids by  
19 UV-Vis spectroscopy affords, in most cases, colorless ionic liquids. The preparation  
20 of colorless ionic liquids is not an easy task for all ionic liquids and several methods  
21 have been recently reported by Seddon and coworkers to purify ionic liquids after  
22 their synthesis for such analytic purposes [75].

### 23 24 25 26 **IR spectroscopy**

27 *In situ* high-pressure infrared spectroscopy has been applied successfully by  
28 Dupont, van Leeuwen and coworkers to probe the catalytically active Rh-complex  
29 in the 1-octene hydroformylation reaction. The active catalyst formed by re-  
30 action of the  $[\text{Rh}(\text{acac})(\text{CO})_2]$  precursor and the ligand 2,7-bissulfonate-4,5-  
31 bis(diphenylphosphino)-9,9-dimethylxanthene (sulfoxantphos) in the ionic liquid  
32  $[\text{BMIM}][\text{PF}_6]$  [76]. These authors found that the *in situ* IR signals were very similar  
33 to the same precursor/ligand mixture in organic solvent, indicating that the same  
34 mixture of ee (bis-equatorial) and ea (equatorial-apical)  $[(\text{diphosphine})\text{Rh}(\text{CO})_2\text{H}]$   
35 catalyst complex is also the active species in the ionic liquid. Later, these data were  
36 used by Riisager and coworkers as a reference to prove the homogeneously dis-  
37 solved character of the same Rh-complexes in supported ionic liquid phase (SILP)  
38 catalytic systems [35].

### 39 40 41 **EPR spectroscopy**

42 EPR spectroscopy has been applied by Kucheroov and coworkers to study the nature  
43 of the catalytically active species in  $[\text{W}^{n+}(\text{Mo}^{n+}) - \text{ionic liquids} - \text{olefin}]$  metathesis  
44 systems [77]. In this study the key role of isolated paramagnetic complexes of  $\text{W}^{5+}$   
45 and  $\text{Mo}^{5+}$  ions in the catalytic metathesis of 1-hexene could be demonstrated. It

1 was shown that the number of EPR-visible isolated paramagnetic  $\text{Mo}^{5+}$  complexes  
2 in the ionic liquid reaches around 90% of the total number of molybdenum ions  
3 in the melt. Furthermore it was shown that the kinetics of the metathesis reaction  
4 correlates closely with the initial reduction of  $\text{W}^{6+}$  to  $\text{W}^{5+}$  species.

#### 5 *Mass spectroscopy*

6  
7 Many catalyst complexes that are suitable for operation and immobilization in ionic  
8 liquids are ionic themselves with the charge either located at the metal center or in  
9 the ligand sphere. Thus, these complexes are accessible to electrospray ionization  
10 mass spectroscopy (ESI-MS). However, it is not a trivial task to investigate an  
11 ionic catalyst complex next to the vast excess of ionic liquid ions. Dyson's group  
12 reported a combination of ESI-MS with quadrupole ion trap methods that enabled  
13 the detection of, e.g. several cationic Rh-complexes in the ionic liquid [BMIM][PF<sub>6</sub>]  
14 [62]. They could demonstrate that the detection limit of their methodology (catalyst  
15 concentrations down to  $1 \times 10^{-10} \text{ mol l}^{-1}$  were analyzed) is so low that even  
16 complexes in the typically very low concentration of a catalytic experiment could be  
17 easily characterized, even in the presence of a large excess of ionic liquid ions.

18 It should be noted here that MS techniques have been used with great success in  
19 the recent past to study species dissolved in ionic liquids [78] as well as the aggregate  
20 formation of ionic liquid ions in different ion mixtures [79] and in the presence of  
21 organic solvents [80], impressively underlining the potential of mass spectrometry  
22 for ionic liquid investigation in a more general respect.

#### 23 *Extended X-ray absorbance fine structure (EXAFS) spectroscopy*

24  
25 EXAFS studies have been among the first analytical techniques applied to study  
26 metal complexes dissolved in ionic liquids or melts containing metallate anions [65]  
27 and more recent examples can also be found in the literature [81]. However, the num-  
28 ber of attempts to apply this well established and very successful methodology to the  
29 study of metal complexes in direct context with catalytic reactions is relatively small.

30 Iwasawa and coworkers published, for example, Suzuki cross-coupling reactions  
31 using [BMIM]<sub>2</sub>[NiCl<sub>4</sub>] as the catalyst precursor [82]. By applying EXAFS analysis  
32 they could conclude that the active catalyst obtained after treatment of the precursor  
33 with  $\text{K}_3\text{PO}_4$  or  $\text{NaO}^t\text{Bu}$  is indeed the corresponding carbene complex. The analyzed  
34 catalytic systems proved to be highly active and selective in the cross-coupling  
35 reaction of aryl chlorides with arylboronic acids in the presence of two equivalents  
36 of  $\text{PPh}_3$ . Another example of the successful application of EXAFS studies for the  
37 direct study of catalytic active species in ionic liquids has been reported by Dupont  
38 and coworkers [83]. These authors investigated the reduction of  $[\text{Ir}(\text{cod})\text{Cl}]_2$  (cod =  
39 1,5-cyclooctadiene) dissolved in different [BMIM] ionic liquids in the presence of  
40 1-decene to yield Ir(0) nanoparticles. Their EXAFS analyses (in combination with  
41 *in situ* TEM, SAXS, XPS and XRD of the isolated material) provided evidence  
42 for interactions of the ionic liquid with the metal surface and demonstrated the  
43 formation of an ionic liquid protective layer surrounding the iridium nanoparticles.  
44  
45

1 In an earlier publication the same authors had reported the catalytic activity of these  
2 Ir nanoparticles in the hydrogenation of several olefinic substrates [84].

### 3 4 **XPS spectroscopy**

5 A technique that has only very recently been introduced but promises great po-  
6 tential for the investigation of transition metal catalysts in ionic liquids is X-ray  
7 photoelectron spectroscopy (XPS). XPS is a highly surface sensitive method able  
8 to analyse quantitatively the elemental composition of an ionic liquid surface vs.  
9 ultra-high vacuum ( $10^{-10}$  mbar) including the oxidation state of the observed ele-  
10 ments. Licence and coworkers pioneered this method for ionic liquids by studying  
11  $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$  at the surface of the ionic liquid  $[\text{EMIM}][\text{EtOSO}_3]$  [85]. They were  
12 able to follow spectroscopically the decomposition of the  $\text{Pd(II)}$  complex to form a  
13  $\text{Pd(0)}$  species. Later, Maier et al. expanded the methodology by selective detection  
14 of photoelectrons emitted under different angles to the normal surface [86]. By  
15 this methodology they were able to distinguish the concentration and chemical na-  
16 ture of Pt-complex ions in the top surface layer from those in the layers beneath.  
17 Very interestingly, by dissolving the complex  $[\text{Pt}(\text{NH}_3)_4]\text{Cl}_2$  in  $[\text{EMIM}][\text{EtOSO}_3]$  a  
18 complete surface depletion of  $\text{Cl}^-$  ions was observed and a surface enrichment of  
19 the soft Pt-complex ions was unambiguously detected. These findings may have  
20 great implications for multiphasic catalysis with ionic liquids as the possibility of an  
21 enrichment of catalyst species may give an important starting point for the interpre-  
22 tation of kinetic data. In more general, XPS spectroscopy of ionic catalyst solutions  
23 has been found to be a very powerful analytic tool that makes elegant use of the  
24 extremely low volatility of the ionic liquid. The methodology may have a substan-  
25 tial impact on the understanding of liquid surfaces in homogeneous catalysis in  
26 general.

27 Of course, the examples described above are not comprehensive. But it is im-  
28 portant to note that the total number of spectroscopic studies to understand better  
29 transition metal catalyzed reactions in ionic liquids is still very small – at least com-  
30 pared to the overall number of papers describing catalytic reactions in ionic liquids.  
31 It is encouraging however, that the number of sound mechanistic studies is now  
32 beginning to increase. Without doubt, much more work of this kind is still needed  
33 to better understand the nature of active catalytic species in ionic liquids and to  
34 explain some of the observed “ionic liquid” effects on a rational level. It will only be  
35 by gaining a thorough understanding of these effects that the true potential of ionic  
36 liquids in transition metal catalysis can be realized.

### 37 38 39 **5.3.2**

#### 40 **Selected Examples of the Application of Ionic Liquids in Transition Metal Catalysis**

##### 41 42 **5.3.2.1 Hydrogenation**

43 The use of ionic liquids has been successfully studied in many transition metal  
44 catalyzed hydrogenation reactions ranging from simple olefin hydrogenation to  
45 examples of asymmetric hydrogenation. Almost all applications so far include proce-

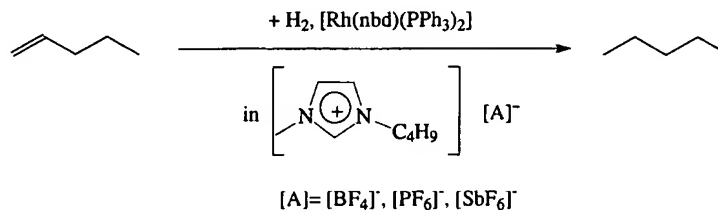
dures of multiphase catalysis with the transition metal complex being immobilized in the ionic liquid by its ionic nature or by means of ionic (or highly polar) ligands.

Hydrogenation, in principle, is very well suited for a biphasic reaction mode using ionic liquids. A large number of known, ionic hydrogenation catalysts are available [87] and the miscibility gap between the saturated reaction products and the ionic liquid is often large so that, in the majority of cases, a biphasic procedure is possible. This allows easy product separation after the reaction with low product solubility in the catalyst phase. Moreover, the formation of heavy, polar side products that would accumulate in the catalyst phase during recycling is not very likely in hydrogenation chemistry.

While the solubility of alkenes in ionic liquids is high enough for most hydrogenation applications (in particular if an appropriate cation design is applied) the hydrogen solubility has been shown to be intrinsically relatively low (see Section 3.3. for more details) [88]. Thus hydrogenation reactions in ionic liquids proceed at low hydrogen concentrations. This is some disadvantage as higher pressures may be required in some cases. However, it is noteworthy that the availability of hydrogen for a hydrogenation reaction results not only from its solubility under equilibrium conditions but reflects as well the ease of its transfer from the gas phase to the melt's surface and into the melt. Since the diffusion of hydrogen into ionic liquids has been found to be relatively fast [89], the latter contribution is of special importance. The high diffusivity of hydrogen results in high hydrogen transfer rates into the catalyst layer so that – during a hydrogenation reaction – the consumed hydrogen can be replenished rapidly. This fact explains the high number of successful hydrogenation reactions that have been reported in ionic liquids (see below) despite the usually low hydrogen solubility in these media.

#### Hydrogenation of olefins

The first transition metal catalyzed hydrogenation reactions in ionic liquids were reported by the groups of de Souza [90] and Chauvin [91] in 1995. De Souza et al. investigated the Rh-catalyzed hydrogenation of cyclohexene in [BMIM][BF<sub>4</sub>]. Chauvin et al. dissolved the cationic "Osborn complex" [Rh(nbd)(PPh<sub>3</sub>)<sub>2</sub>][PF<sub>6</sub>] (nbd=norbornadiene) in ionic liquids with weakly coordinating anions (e.g., [PF<sub>6</sub>]<sup>−</sup>,



**Scheme 5.3-7** Biphasic hydrogenation of 1-pentene with the cationic "Osborn complex" [Rh(nbd)(PPh<sub>3</sub>)<sub>2</sub>][PF<sub>6</sub>] (nbd=norbornadiene) in ionic liquids with weakly coordinating anions.

Table 5.3-1 Rh catalyzed hydrogenation of pent-1-ene.

No.	Solvent	Conversion (%) pent-1-ene	Yield <sup>a</sup> pentane	pent-2-ene	TOF (min <sup>-1</sup> ) <sup>b</sup>
1 <sup>c</sup>	acetone	99	38	61	0.55
2	[BMIM][SbF <sub>6</sub> ]	96	83	13	2.54
3	[BMIM][PF <sub>6</sub> ]	97	56	41	1.72
4	[BMIM][BF <sub>4</sub> ]	10	5	5	0.15

<sup>a</sup> Cat. 0.05 mmol; pent-1-ene: 8.4 mmol; solvent: 4 ml, *T* = 30 °C, *p*(H<sub>2</sub>) = 0.1 MPa; *t* = 2 h.<sup>b</sup> TOF = mol (pentane) per mol (rhodium) and time (min).<sup>c</sup> 10 ml acetone, 9.2 mmol pent-1-ene.

[BF<sub>4</sub>]<sup>-</sup> and [SbF<sub>6</sub>]<sup>-</sup>) and used the ionic catalyst solutions thus obtained according to Scheme 5.3-7 for the biphasic hydrogenation of 1-pentene.

Table 5.3-1 summarizes the most relevant results of this early study. Although the reactants show only limited solubility in the catalyst phase, the rates of hydrogenation in [BMIM][SbF<sub>6</sub>] are almost five times faster than for the comparable reaction in acetone. However, the reaction was found to be much slower using a hexafluorophosphate ionic liquid. This effect was attributed to the better solubility of pentene in the hexafluoroantimonate ionic liquid. The very poor yield in [BMIM][BF<sub>4</sub>], however, was due to a high amount of residual Cl<sup>-</sup> ions in the ionic liquid leading to catalyst deactivation. At that time the preparation of this tetrafluoroborate ionic liquid in a chloride-free quality was obviously a problem.

All ionic catalyst solutions could be reused repeatedly. The loss of rhodium through leaching into the organic phase was below the detection limit of 0.02%. These results are of general importance for the field of biphasic catalysis since this was the first time that a rhodium catalyst could be "immobilized" in a polar solvent without the use of especially designed ligands. Moreover, Chauvin's group described the selective hydrogenation of cyclohexadiene to cyclohexene by making use of the biphasic reaction system [91]. Since the solubility of cyclohexadiene in [BMIM][SbF<sub>6</sub>] is about five times higher than the solubility of cyclohexene in the ionic liquid, the latter was obtained in 98% selectivity at 96% conversion.

Following up these pioneering studies several other papers dealing with non-stereoselective hydrogenations of olefins in ionic liquids using liquid-liquid biphasic systems have been published [92–96]. The immobilization of Pd(acac)<sub>2</sub> as hydrogenation catalyst in the ionic liquids [BMIM][BF<sub>4</sub>] and [BMIM][PF<sub>6</sub>] was reported by Dupont et al. in 2000 [94]. They compared the biphasic hydrogenation of butadiene with the homogeneous system with all reactants being dissolved in CH<sub>2</sub>Cl<sub>2</sub>, with the reaction in neat butadiene and with a heterogeneous system using Pd on carbon as catalyst. The paper demonstrates that for 1,3-butadiene hydrogenation the selectivities achieved with Pd(acac)<sub>2</sub> dissolved in ionic liquids were similar to those observed under homogeneous conditions and were higher than under heterogeneous conditions (using Pd on carbon as the catalyst) or in

neat 1,3-butadiene. The authors extended their investigations to a series of functionalized dienes like sorbic acid, methyl sorbate, 1-nitro-1,3-butadiene, and cyclic dienes.

The group of Dupont also studied the catalytic activity of  $\text{RuCl}_2(\text{PPh}_3)_3$  and  $\text{K}_3\text{Co}(\text{CN})_5$  in  $[\text{BMIM}][\text{BF}_4]$  for the hydrogenation of a number of unfunctionalized, unsaturated hydrocarbon compounds [93]. It was found that – with the ruthenium complex as catalyst – the interaction of  $\text{RuCl}_2(\text{PPh}_3)_3$  with the ionic liquid led to a stable, ionic purple solution, and no leaching of the Ru complex could be detected by extraction with hydrocarbon solvents. Turnover frequencies up to  $537 \text{ h}^{-1}$  were achieved. It is also noteworthy that the hydrogenation in the liquid required less drastic conditions (temperature and hydrogen pressure) compared to the hydrogenation in an aqueous medium using the water-soluble catalyst.

Many low oxidation state transition metal (carbonyl) clusters are salts and can be stabilized in ionic liquids due to their ionic character. Interestingly, Dyson et al. revealed that the activity of certain clusters in the hydrogenation of alkene substrates is up to 3.6-fold faster if these clusters are immobilized in ionic rather than in organic solvents [96]. They evaluated the clusters  $[\text{HFe}(\text{CO})_{11}]^-$ ,  $[\text{HWOs}_3(\text{CO})_{14}]^-$ ,  $[\text{H}_3\text{Os}_4(\text{CO})_{12}]^-$  and  $[\text{Ru}_6\text{C}(\text{CO})_{16}]^{2-}$  as catalysts/pre-catalysts in the hydrogenation of styrene to ethylbenzene in  $[\text{BMIM}][\text{BF}_4]$ , octane and methanol respectively. Using  $[\text{Ru}_6\text{C}(\text{CO})_{16}]^{2-}$  as catalyst precursor in  $[\text{BMIM}][\text{BF}_4]$ , the same research group also obtained good results in the partial reduction of cyclohexadienes to cyclohexene. However, by poisoning the catalytic phase with mercury and by means of high-pressure  $^1\text{H}$ -NMR spectroscopy experiments they revealed that under the reaction conditions Ru-colloids/Ru-nanoparticles were formed and the latter acted as the catalyst in these reactions. These studies represent therefore examples of heterogeneous catalysis with nanoparticles in ionic liquids and will be discussed in more detail in Section 5.3.2.7. In contrast to the ruthenium-containing cluster, a homogeneous hydride complex was found to be the active catalyst with the osmium-containing clusters being dissolved in ionic liquids [96]. A comparison of the turnover frequencies of the  $[\text{H}_3\text{Os}_4(\text{CO})_{12}]^-$ -catalyzed hydrogenation of styrene to ethylbenzene in various ionic liquids is presented in Table 5.3-2.

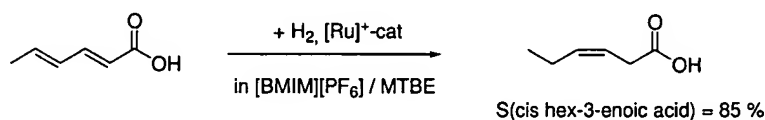
The turnover frequencies in all the ionic liquids are quite similar although the values are somewhat lower in  $[\text{BMMIM}][\text{PF}_6]$ ,  $[\text{BMMIM}][\text{BF}_4]$  and  $[\text{BMMIM}][(\text{CF}_3\text{SO}_2)_2\text{N}]$  than in the  $[\text{BMIM}]$ -containing ionic liquids. The highest activity was found for  $[\text{OMPy}][\text{BF}_4]$  ( $[\text{OMPy}] = 1\text{-octyl-3-methylpyridinium}$ ) being used as the ionic liquid. An explanation for this could be the fact that  $[\text{BMMIM}]$ -containing ionic liquids possess the highest viscosities and have therefore the lowest mass transfer rates for hydrogen. The experiment with  $[\text{OMPy}][\text{BF}_4]$  is special in that only for this ionic liquid does the reaction mixture form a single phase thus preventing any liquid–liquid mass transport resistance. However, this monophasic reaction mode also means that catalyst recycling by simple decantation is not possible in that latter case.

The selective hydrogenation of sorbic acid to *cis*-3-hexenoic acid was demonstrated in ionic liquids by Drießen-Hölscher et al. (Scheme 5.3-8). Based on investigations

**Table 5.3-2** Hydrogenation of styrene to ethylbenzene using  $[\text{H}_3\text{Os}_4(\text{CO})_{12}]^-$  as the catalyst precursor in various ionic liquids.

Ionic liquid	TOF ( $\text{mol mol}^{-1} \text{h}^{-1}$ )
[BMIM][BF <sub>4</sub> ]	587
[BMIM][PF <sub>6</sub> ]	522
[BMIM][(CF <sub>3</sub> SO <sub>2</sub> ) <sub>2</sub> N]	587
[BMMIM][PF <sub>6</sub> ]	392
[BMMIM][BF <sub>4</sub> ]	413
[BMMIM][(CF <sub>3</sub> SO <sub>2</sub> ) <sub>2</sub> N]	457
[OMPy][BF <sub>4</sub> ]	718

Conditions:  $p(\text{H}_2) = 50.7$  bar, 100 °C, 4 h; Cluster concentration  $5 \times 10^{-4}$  M, ionic liquid (1 ml), styrene (1 ml), total reactor volume (30 ml); TOF is the turnover in units of  $\text{mol (product) mol}^{-1} (\text{catalyst}) \text{h}^{-1}$ , calculated as an average value over 4 h.



**Scheme 5.3-8** Regioselective hydrogenation of sorbic acid in the biphasic system [BMIM][PF<sub>6</sub>]/MTBE.

in the biphasic system water/*n*-heptane [97], the ruthenium-catalyzed reaction was studied in the biphasic system [BMIM][PF<sub>6</sub>]/MTBE [98].

In comparison to an optimized polar organic solvent (e.g. glycol) a more than threefold increase in activity with comparable selectivity to *cis*-3-hexenoic acid was observed in the ionic liquid. This is explained by a partial deactivation (through complexation) of the catalytic active center in those polar organic solvents that are able to dissolve the cationic Ru-catalyst. In contrast, the ionic liquid [BMIM][PF<sub>6</sub>] is known to combine high solvation power for ionic metal complexes with relatively weak coordination strength. In this way the catalyst can be dissolved in a "more innocent" environment than is the case if polar organic solvents are used. After the biphasic hydrogenation of sorbic acid, the ionic catalyst solution could be recovered by phase separation and reused four times with no significant loss of selectivity but a decreasing conversion from 74.0 and 77.4%, to 59.6 and 35.8% in the third and fourth run. However, during these recycling experiments the autoclave containing the catalyst phase had to stand overnight between the second and the third run.

#### Hydrogenation of arenes

The hydrogenation of arenes is industrially important, but so far is dominated by the use of heterogeneous catalysts. Ionic liquids offer, in principle, the chance to use a liquid–liquid biphasic system where the homogeneous catalyst is immobilized and therefore recyclable. Dyson et al. applied ruthenium clusters as catalyst for

## 394 | 5 Organic Synthesis

Table 5.3-3 Comparative studies of the biphasic hydrogenation reactions of arenes in [BMIM][BF<sub>4</sub>] and water with [H<sub>4</sub>Ru<sub>4</sub>( $\eta^6$ -C<sub>6</sub>H<sub>6</sub>)<sub>4</sub>][BF<sub>4</sub>]<sub>2</sub> as the catalyst precursor.

Substrate	Reaction system	Reaction conditions	Conversion (%)	Catalytic turnover <sup>a</sup> /h <sup>-1</sup>
benzene	ionic liquid	60 atm H <sub>2</sub> , 90 °C, 2.5 h	91	364
	water	60 atm H <sub>2</sub> , 90 °C, 2.5 h	88	352
toluene	ionic liquid	60 atm H <sub>2</sub> , 90 °C, 3 h	72	240
	water	60 atm H <sub>2</sub> , 90 °C, 3 h	78	261
cumene	ionic liquid	60 atm H <sub>2</sub> , 90 °C, 2.5 h	34	136
	water	60 atm H <sub>2</sub> , 90 °C, 2.5 h	31	124

<sup>a</sup>Catalytic turnover is calculated on the assumption that the tetraruthenium catalyst does not break down into monoruthenium fragments, which is entirely consistent with the data.

the hydrogenation of benzene, toluene, cymene, ethylbenzene and chlorobenzene [99, 100]. A direct comparison of the two biphasic systems water/organic solvent and ionic liquid/organic solvent showed that the turnover frequencies obtained in the ionic liquid and the aqueous media are similar [99]. The results of hydrogenation in the two biphasic systems are shown in Table 5.3-3. The authors propose, that the catalytical active species is [H<sub>6</sub>Ru<sub>4</sub>( $\eta^6$ -C<sub>6</sub>H<sub>6</sub>)<sub>4</sub>]<sup>2+</sup> in the ionic liquid-containing system, as was shown for the water-containing system [100]. Again the advantage of the ionic liquid-containing biphasic system was the easy separation of products and the possibility to reuse the catalytic active phase.

Very interesting results were obtained by using [Ru( $\eta^6$ -p-cymene)( $\eta^2$ -TRIPHOS)Cl][PF<sub>6</sub>] in a biphasic system with [BMIM][BF<sub>4</sub>] as catalyst phase [101]. Hydrogenation of benzene, toluene and ethylbenzene in this ionic liquid proceeded with higher yields and accordingly with higher turnover frequencies than in the monophasic system with CH<sub>2</sub>Cl<sub>2</sub> as solvent. The TOF (yield) of benzene hydrogenation was found to increase from 242 h<sup>-1</sup> (52% yield) in CH<sub>2</sub>Cl<sub>2</sub> to 476 h<sup>-1</sup> (82% yield) in the ionic liquid, for toluene from 74 h<sup>-1</sup> (19% yield) to 205 h<sup>-1</sup> (42% yield) and for ethylbenzene from 57 h<sup>-1</sup> (17% yield) to 127 h<sup>-1</sup> (30% yield), respectively. With allylbenzene as the substrate the authors observed selective hydrogenation of the benzyl group and the unsaturated alkyl chain remained intact. The hydrogenation yielded allylcyclohexane with a TOF of 329 h<sup>-1</sup> (84% yield), whereas the system was inactive toward arenes with R-alkene substituents such as styrene and 1,3-divinylbenzene.

#### Hydrogenation of polymers

Transition metal catalyzed hydrogenation in ionic liquids has also been applied to the hydrogenation of polymers. First studies were presented by Dupont's group which investigated the hydrogenation of acrylonitrile-butadiene copolymers [102]. These early studies were later expanded by Rosso and coworkers studying the rhodium catalyzed hydrogenation of polybutadiene (PBD), nitrile-butadiene rubber (NBR) and styrene-butadiene rubber (SBR) in a [BMIM][BF<sub>4</sub>]/toluene and a



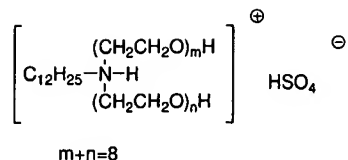


Fig. 5.3-5 Structure of a polyether-modified ammonium salt ionic liquid as used for the hydrogenation of polystyrene-*b*-polybutadiene-*b*-polystyrene (SBS) block copolymer using a Ru/TPPTS catalyst.

[BMIM][BF<sub>4</sub>]/toluene/water system [103]. The activity of the catalyst followed the trend PBD > NBR > SBR, which corresponds to the order of polymer solubility in the ionic liquid. The degree of hydrogenation (as a percent of total hydrogenation) was 94% for PBD (4 h reaction time), 43% for NBR (4 h reaction time), and 19% for SBR (3 h reaction time).

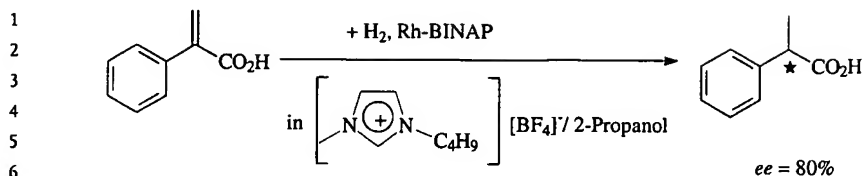
A polyether modified ammonium salt ionic liquid/organic biphasic system was used by Jiang et al. for the hydrogenation of polystyrene-*b*-polybutadiene-*b*-polystyrene (SBS) block copolymer using a Ru/TPPTS complex as catalyst [104]. The ionic liquid is displayed in Fig. 5.3-5.

By addition of triphenylphosphine as promoter ligand, hydrogenation degrees of up to 89% could be achieved. Hydrogenation of the benzene ring and gel formation was not observed. The active catalyst was found to be well immobilized in the ionic liquid and the ionic catalyst phase could be reused three times without significant loss in catalytic activity.

#### Stereoselective hydrogenation

Since 1995 a number of enantioselective hydrogenation reactions have been described using ionic liquids as the catalyst immobilization phase. In most cases reported so far the role of the ionic liquid was solely to allow facile recycling of the expensive chiral metal complex by liquid-liquid operation. Again, Chauvin et al. pioneered the field describing the hydrogenation of  $\alpha$ -acetamido cinnamic acid using [Rh(cod)(-)-(diop)][PF<sub>6</sub>] as catalyst in a [BMIM][SbF<sub>6</sub>] melt affording (S)-phenylalanine with 64% enantiomeric excess (*ee*) [91]. The product was easily and quantitatively separated and the ionic liquid could be recovered. The loss of rhodium was less than 0.02% per run. Dupont and coworkers were able to obtain up to 80% *ee* in the reaction of 2-arylacrylic acid to (S)-2-phenylpropionic acid with the chiral [RuCl<sub>2</sub>(S)-BINAP]<sub>2</sub>NEt<sub>3</sub> complex as catalyst in [BMIM][BF<sub>4</sub>] melts (Scheme 5.3-9) [105]. Both reactions were carried out in two phases with the help of an additional organic solvent (e.g. iPrOH).

In another example de Souza and Dupont studied the asymmetric hydrogenation of  $\alpha$ -acetamido cinnamic acid and the kinetic resolution of ( $\pm$ )-methyl-3-hydroxy-2-methylenebutanoate with chiral Rh(I) and Ru(II) complexes in [BMIM][BF<sub>4</sub>] and [BMIM][PF<sub>6</sub>] [106]. A special focus of their work was on the influence of H<sub>2</sub> pressure on conversion. They determined the hydrogen solubility in the ionic liquid using



**Scheme 5.3-9** Hydrogenation of 2-arylacrylic acid to (S)-2-phenylpropionic acid with the chiral  $[\text{RuCl}_2(\text{S})\text{-BINAP}]_2\text{NEt}_3$  complex as catalyst in  $[\text{BMIM}][\text{BF}_4]$ .

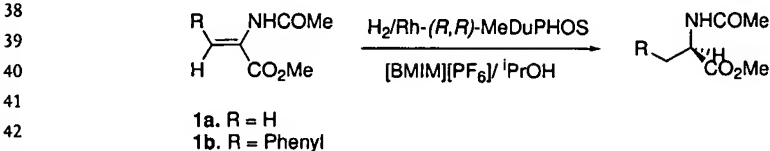
pressure drop experiments [107]. The solubility values reported are  $K = 3.0 \times 10^{-3} \text{ mol L}^{-1} \text{ atm}^{-1}$  for  $\text{H}_2$  in  $[\text{BMIM}][\text{BF}_4]$  and  $8.8 \times 10^{-4} \text{ mol L}^{-1} \text{ atm}^{-1}$  for  $\text{H}_2$  in  $[\text{BMIM}][\text{PF}_6]/\text{H}_2$  at room temperature. These values differ significantly from those determined by Dyson et al. using  $^1\text{H-NMR}$  [88b]. The reported values suggest that molecular hydrogen is almost four times more soluble in  $[\text{BMIM}][\text{BF}_4]$  than it is in  $[\text{BMIM}][\text{PF}_6]$  under the same pressure. According to the authors, this difference in solubility leads to the different degrees of conversion observed in their experiments. They reported 73% conversion (93% *ee*) for the reaction in  $[\text{BMIM}][\text{BF}_4]$  while only 26% conversion (81% *ee*) was found using  $[\text{BMIM}][\text{PF}_6]$  as reaction medium (50 bar hydrogen pressure in both experiments).

Geresh et al. applied the chiral rhodium complex  $[\text{Rh-MeDuPHOS}]$  dissolved in  $[\text{BMIM}][\text{PF}_6]$  for the asymmetric hydrogenation of enamides [108] (Scheme 5.3-10). The group focussed on the stabilization of the air-sensitive catalyst in the ionic liquid and described the ionic liquid as being able to protect the air-sensitive complex from attack by atmospheric oxygen. According to the authors this greatly facilitates recycling of the ionic catalyst solution.

The catalytic results were comparable to those of the homogeneous reaction in *i*PrOH and recyclability could be demonstrated over five cycles with constant *ee* though decreasing conversion. Amazingly the catalyst still showed some catalytic activity after storage under atmospheric conditions for 24 h.

In enantioselective hydrogenation substrates can be divided into two classes (Fig. 5.3-6): Class I are substrates which require low  $\text{H}_2$  pressure to obtain good enantioselectivities while class II substrates require high  $\text{H}_2$  pressure [109, 110].

In this context the group of Jessop studied the influence of different ionic liquids in the asymmetric hydrogenation of representatives from both classes



**Scheme 5.3-10** Asymmetric hydrogenation of enamides catalyzed by Rh-MeDuPHOS immobilized in  $[\text{BMIM}][\text{PF}_6]$ .

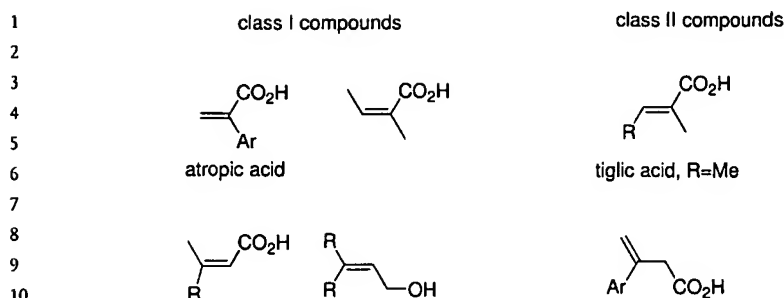


Fig. 5.3-6 Classification of substrates for enantioselective hydrogenation.

[111]. Atropic acid was investigated as an example of class I compounds and the hydrogenation of tiglic acid was selected as an example of class II compounds. For atropic acid a strong dependence of the obtained  $ee$  on the used solvent was found. The  $ee$  values varied in the range of 72% to 95% increasing in the following order:  $\text{MeOH} < [\text{EMIM}][\text{CF}_3\text{SO}_3] < [\text{BMIM}][\text{BF}_4] = [\text{MBPy}][\text{BF}_4] < [\text{BMIM}][\text{PF}_6] = [\text{MMPIM}][(\text{CF}_3\text{SO}_2)_2\text{N}]$  ( $[\text{MMPIM}] = 1,2\text{-dimethyl-3-propylimidazolium}$ )  $< [\text{EMIM}][(\text{CF}_3\text{SO}_2)_2\text{N}]$ . In contrast, enantioselectivities were low for the asymmetric hydrogenation of the class II substrate in ionic liquids (without co-solvent). The best enantioselectivities were obtained using methanol as co-solvent. This effect is presumably due to the reduction of viscosity with methanol addition (i.e. enhanced mass transfer) and increased hydrogen solubility compared to pure ionic liquids. For the reactions in neat ionic liquids, the selectivity was found to depend on the choice of ionic liquid, now increasing in the order:  $[\text{BMIM}][\text{BF}_4] < [\text{EMIM}][\text{O}_3\text{SCF}_3] < [\text{BMIM}][\text{PF}_6] = [\text{EMIM}][(\text{CF}_3\text{SO}_2)_2\text{N}] < [\text{MMPIM}][(\text{CF}_3\text{SO}_2)_2\text{N}]$ . Remarkably these results demonstrate that the effectiveness of these asymmetric hydrogenations in ionic liquids is not only a function of  $\text{H}_2$  availability. Many solvent parameters including polarity, coordinating ability and hydrophobicity have to be taken into account and add to a complex picture that is still not fully understood.

Attempts to improve the solubility and immobilization of chiral hydrogenation catalysts in ionic liquids were presented by Lee and coworkers [112]. They synthesized a chiral Rh-complex carrying the dicationic bisphosphine ligand depicted in Fig. 5.3-7. Immobilization of the tricationic complex in  $[\text{BMIM}][\text{SbF}_6]$  showed better immobilization results in contact with  $i\text{PrOH}$  compared to the non-modified complex Me-BDPMI in the Rh-catalyzed asymmetric hydrogenation of  $N\text{-acetylphenylethanamine}$  (Scheme 5.3-11). The ionic catalyst solution was reused three times without loss of activity. In the fourth run conversion decreased but high conversions could still be realized by increasing the reaction time.

Finally, a broad screening of ligands and ionic liquids was carried out by Feng et al. for the Rh-catalyzed hydrogenation of enamides [113]. Rhodium-ferrocenyl-diphosphine complexes with taniaphos, josiphos, walphos and mandyphos

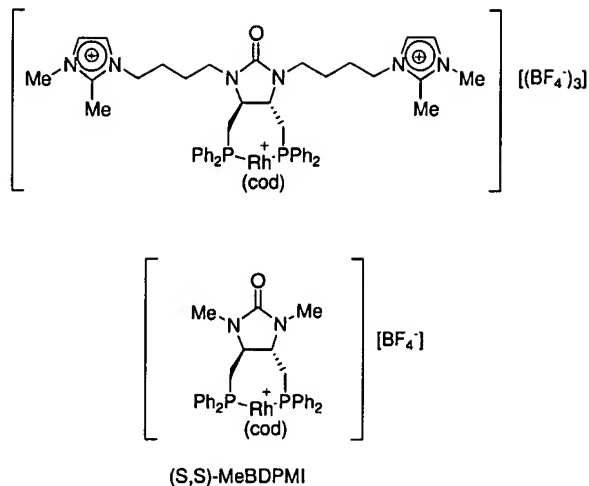
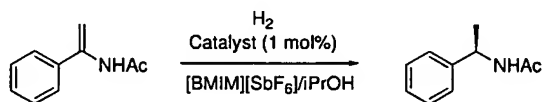


Fig. 5.3-7 Rh-complex with a bisphosphine-containing cation as ligand.

Scheme 5.3-11 Rh-catalyzed asymmetric hydrogenation of *N*-acetylphenylethanamine.

ligands were identified in this study to be the most effective catalyst complexes (see Fig. 5.3-8).

The screening of the different reaction media proved that the application of an ionic liquid/water mixture – a so-called “wet ionic liquid” – led to improved catalyst recycling compared to the reaction in ionic liquid without co-solvent. This comparative study revealed good results for the hydrogenation of various enamides in wet ionic liquids with respect to conversion, enantioselectivity and catalyst separation. The results obtained with the Rh-taniaphos system in different solvent systems are summarized in Table 5.3-4.

#### Ketone and imine hydrogenation in ionic liquids

There is only one study on ketone hydrogenation in ionic liquids which applied Rh-complexes as catalysts. Zhu et al. synthesized a new carborane-based room-temperature ionic liquid consisting of an *N*-*n*-butylpyridinium cation and the anion  $[\text{CB}_{11}\text{H}_{12}]^-$ , and used this ionic liquid as the reaction medium in the asymmetric hydrogenation of unsymmetrical aryl ketones in the presence of the chelating ligand (*R*)-BINAP and a rhodacarborane catalyst (Table 5.3-5) [114]. Compared to hydrogenation in tetrahydrofuran and in “classical” ionic liquids the best results were indeed achieved with the carborane-based ionic liquid.

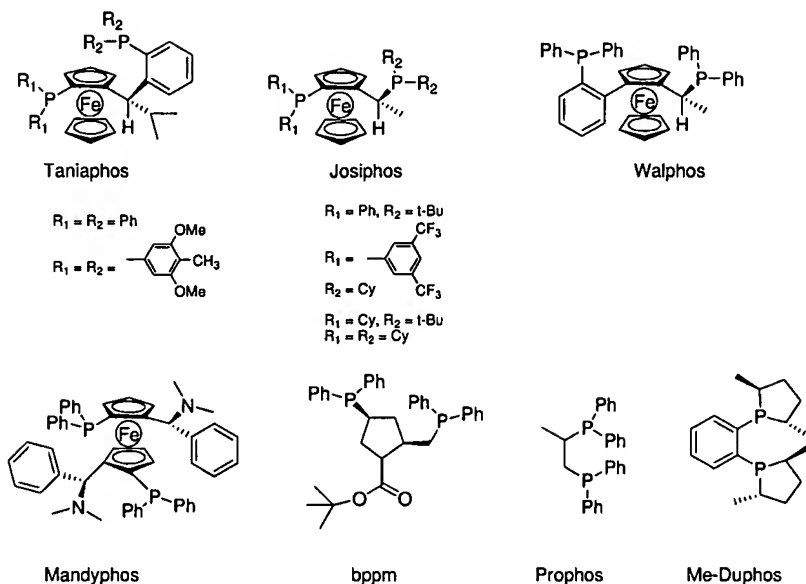


Fig. 5.3-8 Structures of ligands as used for the Rh-catalyzed asymmetric hydrogenation of enamides in ionic liquids.

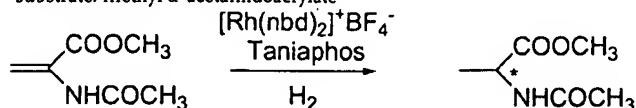
Lin et al. studied the hydrogenation of  $\beta$ -aryl ketoester using a Ru-BINAP system with different substituents at the 4,4'-position of the BINAP ligand [115]. Best enantioselectivities were achieved with sterically demanding and electron-donating 4,4'-substituents. For example, *ee* values of 97.2% and 99.5% were obtained for the hydrogenation of ethyl benzoylacetate with R = trimethylsilane (1, Fig. 5.3-9), and R = bisphosphonic acid (2, Fig. 5.3-9), respectively as substituents. By immobilization of these catalysts in [BMIM][BF<sub>4</sub>], a slight deterioration in *ee* values (reduction of *ee* by 1%) was observed for the trimethylsilane substituted catalyst, while an increase (increase of *ee* by up to 2.6%) was observed for the bisphosphonic acid substituted catalyst. Both catalysts were recycled and reused four times and the *ee* (conversion) decreased from 97.3% (>98% conversion) to 95.1% (62% conversion) in the case of trimethylsilane as substituent and from 97.5% (98% conversion) to 74.7% (44% conversion) for the bisphosphonic acid-substituted catalyst. In both cases no significant leaching was detected. Higher conversions with comparable *ee* were achieved by using [MMPIM][(CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>N] as ionic liquid [116]. These findings can be explained by the absence of the anions [BF<sub>4</sub>]<sup>-</sup> and [PF<sub>6</sub>]<sup>-</sup> (with their potential to liberate the catalyst poison F<sup>-</sup> in a hydrolysis reaction) and the substitution of the acidic proton at the 2-position of the imidazolium cation by a methyl group, which safely prevents carbene formation with the transition metal.

## 400 | 5 Organic Synthesis

Table 5.3-4 Enantioselective hydrogenation of enamides catalyzed by Rh-taniaphos ( $R^1 = R^2 = \text{Ph}$ ) in various ionic liquids/water combinations and in conventional solvents.

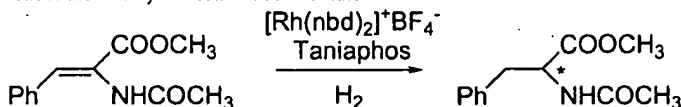
No Reaction medium Conversion (%) ee (%) Catalyst separation No. of phase

substrate: methyl  $\alpha$ -acetamidoacrylate



1	MeOH·H <sub>2</sub> O <sup>a</sup>	100	98	—	1
2	MeOH	100	97	—	1
3	i-PrOH	92	95	—	1
4	toluene	47	28	—	1
5	[BMIM]BF <sub>4</sub>	32	>99	—	1
6	[BMIM]PF <sub>6</sub>	6	91	—	1
7	[BMIM]BF <sub>4</sub> /i-PrOH	64	96	+	2
8	[BMIM]PF <sub>6</sub> /i-PrOH	12	93	+	2
9	[OMIM]BF <sub>4</sub> /H <sub>2</sub> O	100	>99	++	2
10	[BMIM]Tf <sub>2</sub> N/H <sub>2</sub> O	97	>99	++	2
11	[BMIM]BF <sub>4</sub> ·H <sub>2</sub> O <sup>b</sup> /toluene	100	>99	++	2

substrate: methyl  $\alpha$ -acetamidocinnamate



20	i-PrOH	100	94	—	1
21	[BMIM]BF <sub>4</sub>	52	93	—	1
22	[BMIM]BF <sub>4</sub> /i-PrOH	100	93	+	2
23	[OMIM]BF <sub>4</sub> /H <sub>2</sub> O	100	95	++	2
24	[BMIM]BF <sub>4</sub> ·H <sub>2</sub> O <sup>b</sup> /toluene	100	94	++	2
25	[OMIM]BF <sub>4</sub> /H <sub>2</sub> O <sup>c</sup> /toluene	100	95	++	3

<sup>a</sup> ILs: ca. 2 mL, co-solvents: ca. 2–3 mL, S/C = 200, [S] = 0.25 M in co-solvent, room temperature,  $p(\text{H}_2) = 1$  bar, and  $t = 20$  min.

<sup>b</sup> “—” no, “+” good (some leaching), “++” excellent (no leaching).

<sup>c</sup> a v:v = 4:1. b v:v = 6:1. c v:v = 3:1. \* ICP-MS: 0.9 ppm Rh content in co-solvent.

The same catalyst was used in the asymmetric hydrogenation of  $\beta$ -keto esters in [BMIM][PF<sub>6</sub>], [BMIM][BF<sub>4</sub>] and [MMPIM][(CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>N] with complete conversions and ee values of up to 99.3% [117].

Other substituted derivatives of BINAP were investigated by Vaultier et al. [118]. The ammonium salt catalysts (3, Fig. 5.3-9) and (4, Fig. 5.3-9) were prepared *in situ* from the respective bromohydrates and [Ru( $\eta^3$ -2-methylallyl)<sub>2</sub>( $\eta^2$ -COD)] and were immobilized in several ionic liquids. Comparative studies of the hydrogenation of ethyl acetoacetate revealed best results for imidazolium and pyridinium containing ionic liquids. In contrast, no significant ee was observed with the phosphonium

Table 5.3-5 Rh-catalyzed hydrogenation of acetophenone (A) and ethyl benzoylformate (B).<sup>a</sup>

Solvent	Conversion (%) <sup>b</sup>	ee (%) <sup>a</sup>	TOF (h <sup>-1</sup> ) <sup>d</sup>
[OMIM][BF <sub>4</sub> ]	100 (A,B)	97.3(A), 99.3(B)	194(A), 201(B)
[BMIM][BF <sub>6</sub> ]	100 (A,B)	97.8(A), 98.2(B)	207(A), 213(B)
[BPy][CB <sub>10</sub> H <sub>12</sub> ]	100 (A,B)	99.1(A), 99.5(B)	239(A), 306(B)
tetrahydrofuran	82 (A), 87 (B)	91.3(A), 85.7(B)	96(A), 107(B)

<sup>a</sup>Mol ratio of catalyst/(R)-binap/acetophenone = 1:1.5:1000; reaction conditions: H<sub>2</sub> (12 atm), 50 °C, 12 h; [cat.] = 8.1 × 10<sup>-4</sup> M.

<sup>b</sup>Determined by GC.

<sup>c</sup>Determined by GC on a Chirasil DEX CB column.

<sup>d</sup>Turnover frequency (=moles of hydrogenation product per mole of Rh per hour) was determined after 3 h.

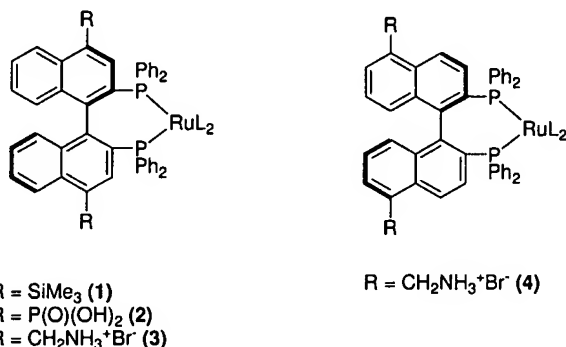


Fig. 5.3-9 Ligands as used in the Ru-catalyzed hydrogenation of  $\beta$ -aryl ketoester in different ionic liquids.

salt. This observation was attributed to problems of solubility and to the ability of complexation for the phosphonium ion. With respect to the selection of anion [BF<sub>4</sub>]<sup>-</sup> appeared superior to [PF<sub>6</sub>]<sup>-</sup> and [(CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>N]<sup>-</sup>.

Ionic liquids have also been applied in transfer hydrogenation. Ohta et al. examined the transfer hydrogenation of acetophenone derivatives with a formic acid–triethylamine azeotropic mixture in the ionic liquids [BMIM][PF<sub>6</sub>] and [BMIM][BF<sub>4</sub>] [119]. They compared the TsDPEN-coordinated Ru(II) complexes (1, Fig. 5.3-10) with the ionic catalyst which was synthesized from the task specific ionic liquid (2, Fig. 5.3-10) in the presence of [RuCl<sub>2</sub>(benzene)]<sub>2</sub>.

The enantioselectivities obtained with the catalyst immobilized by the task specific ionic liquid 2 in [BMIM][PF<sub>6</sub>] were found to be comparable with those of the TsDPEN-coordinated Ru(II) catalyst 1 and reached 93%. Both systems could be recycled five times with only a slight decrease in conversion in cycles 4 and 5 for the TsDPEN-coordinated Ru(II) catalyst 1. The recycling results are displayed in Table 5.3-6.

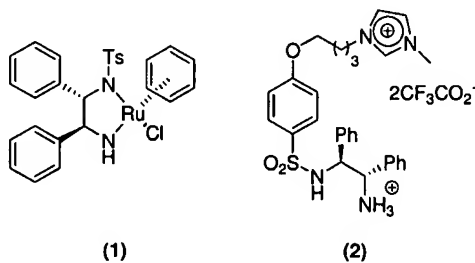
**Table 5.3-6** Recycling of 1 and 2-Ru (Fig. 5.3-10) in the asymmetric transfer hydrogenation of acetophenone using the formic acid–triethylamine azeotropic mixture in the ionic liquids [BMIM][PF<sub>6</sub>].

Cycle	Catalyst 1		Catalyst 2-Ru <sup>a</sup>	
	Conversion (%) <sup>b</sup>	ee (%) <sup>b</sup>	Conversion (%) <sup>b</sup>	ee (%) <sup>b</sup>
1	96	93	98	92
2	99	92	> 99	93
3	95	92	99	93
4	88	92	92	93
5	63	93	75	90

**Reaction conditions:** room temperature, 24 h and S/C = 100.

<sup>a</sup> A mixture of 2 and [RuCl<sub>2</sub>(benzene)]<sub>2</sub> was used.

<sup>b</sup> Determined by capillary GLC analysis using a chiral Cyclodex-B column.



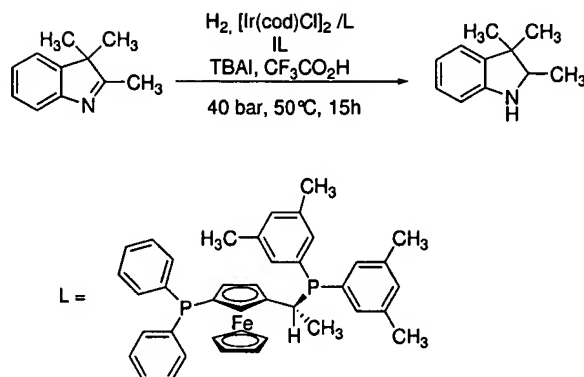
**Fig. 5.3-10 Ru-complex and task specific ionic liquid for the transfer hydrogenation of acetophenone derivatives using a formic acid–triethylamine azeotropic mixture.**

Very few examples of imine hydrogenation in ionic liquids have been published so far. Giernoth et al. screened eight different ionic liquids (the cations were [BMIM]<sup>+</sup>, 1-decyl-3-methylimidazolium ([DMIM]<sup>+</sup>), *N*-butyl-3-methylpyridinium ([BMPy]<sup>+</sup>) and *N*-decyl-3-methylpyridinium ([DMPy]<sup>+</sup>) combined with the anions [BF<sub>4</sub>]<sup>-</sup> and [(CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>N]<sup>-</sup>) and compared them with toluene as solvent in the hydrogenation of trimethylindolenine with the Ir-XYLIPHOS catalyst system (Scheme 5.3-12) [120].

Besides the immobilization of the catalyst, the authors claim, as benefit of the ionic liquids, a reduction of the reaction time from 23 h in toluene to less than 15 h in [DMIM][BF<sub>4</sub>] with no loss in selectivity, although the ionic media require slightly higher reaction temperatures. Furthermore, a stabilization of the ionic catalyst solution against atmospheric oxygen is observed. This stabilization effect facilitates the transfer of freshly prepared catalyst to the autoclave and, in general, makes the handling of the ionic liquid/catalyst system much easier.

Summarizing the actual state of the art it can be stated that the application of ionic liquid media for catalytic hydrogenation has been successfully demonstrated





**Scheme 5.3-12** Enantioselective hydrogenation of trimethylindolenine using Ir-XYLIPHOS as catalyst.

for many substrates and reactions ranging from simple olefin hydrogenation to examples of asymmetric hydrogenation. Almost all applications so far include procedures of multiphase catalysis with the transition metal complex being immobilized in the ionic liquid. Furthermore it was found by far the most authors that activity and selectivity of known transition metal complexes does not change too much in the ionic environment, indicating weak interaction of the ionic liquid ions and the catalyst complex in most cases. Selectivity optimization based on ligand design – especially important in asymmetric catalysis – has been proven many times to work in the same manner in the ionic liquid environment as in an organic solvent. However, some important differences from the homogeneous reactions in organic solvents have to be taken into account. Hydrogen solubility in ionic liquids is very low compared to most traditional solvents so that hydrogen concentration is low at the catalytic center. Mass transfer of hydrogen into the catalyst layer is affected by the viscosity of the ionic liquid (with low viscosities enhancing mass transfer) but has been found to be fast enough in most cases to reach acceptable reaction rates, comparable to those obtained in organic media.

Finally, it should be mentioned that apart from liquid–liquid biphasic mode, catalytic hydrogenation reactions have been carried out with great success in ionic liquid/compressed  $\text{CO}_2$  [111, 112] and supported ionic liquid phase (SILP) systems [122]. In both cases the advantages of a molecular defined, homogeneously dissolved hydrogenation catalyst have been combined with very efficient, continuous processing of the catalytic system. Due to the increasing importance of both fields separate sections of this book have been dedicated to both concepts (see Section 5.5 for ionic liquid/compressed  $\text{CO}_2$  and Section 5.6 for SILP catalysis) and related hydrogenation examples are described there in more detail.

### 5.3.2.2 Oxidation Reactions

Catalytic oxidation reactions in ionic liquids have attracted strong interest in recent years. This is not surprising, taking into account the oxidation stability of ionic liquids well known from electrochemical studies [11] and the great commercial importance of oxidation reactions. Moreover, for oxidation reactions with oxygen the non-volatility of the ionic liquid is of real advantage for safety issues. While the application of volatile organic solvents may be restricted by the formation of explosive mixtures in the gas phase this problem does not arise if a non-volatile ionic liquid is used as the solvent. However, along with these very attractive conceptual features of oxidation chemistry in ionic liquids come two principal problems. First, oxygen solubility in most ionic liquids is relatively low [123], meaning that only a small amount of oxygen is available at the catalytic active center for reaction. Second, the polarity of the oxidation product is usually much higher than the polarity of the starting material, making extraction from the ionic liquid sometimes difficult (a convincing solution to this problem is to work in a hydrophobic ionic liquid and to extract the product into water). Since, additionally, almost all preparative oxidations lead to a product of a higher boiling point compared to the feedstock, product recovery by evaporation can be difficult. The field has been recently reviewed in detail by Muzart [124].

First attempts to use ionic liquids in transition metal catalyzed oxidation reactions were described by Howarth et al. in 2000. They oxidized various aromatic aldehydes to the corresponding carboxylic acids using  $\text{Ni}(\text{acac})_2$  dissolved in  $[\text{BMIM}][\text{PF}_6]$  as the catalyst and oxygen at atmospheric pressure as the oxidant [125]. However, this reaction cannot be considered as a real challenge. Moreover, the catalyst loading used for the described reaction was rather high (3 mol%). The same combination of catalyst, ionic liquid and oxidant has also been used in the synthesis of ethylbenzene hydroperoxide from ethylbenzene [126]. However, in this case it is more accurate to describe the reaction system as a solution of the catalyst and ionic liquid in ethylbenzene. The two principal advantages of the ionic liquid are that it has a greater solubility in the ethylbenzene and the poorly coordinating anion competes less well for the metal center than the previously used tetraalkylammonium halide salts. A more recent attempt to oxidize aldehydes to acids using  $\text{MeReO}_3$  in 1-butyl-3-methylimidazolium ionic liquids with aqueous  $\text{H}_2\text{O}_2$  as oxidizing agent has been reported by Bernini et al. [127].

Many examples have been published demonstrating the feasibility of ionic liquid media for the transition metal catalyzed oxidation of alcohols to ketones. An overview is given in Table 5.3-7.

These publications demonstrate that there is no limitation on the applicability of the ionic liquid methodology concerning the sort of alcohol. Nearly all oxidations in ionic liquids given in Table 5.3-7 were tested with primary, secondary, allylic, benzylic alcohols and phenols with good results. Ruthenium with its high number of accessible oxidation states is a very suitable metal for oxidation reactions in ionic liquids (Table 5.3-7, entries 1–3). As an additional benefit it can be used in the form of its perruthenate salt. Thus immobilization and possibly stabilization of the metal is feasible. It should be mentioned that these oxidation reactions have been reported

Table 3.3-7 Oxidation reactions of alcohols in ionic liquids.

Entry	Catalyst	Ionic liquid	Oxidizing agent	Ref.
1	tetra- <i>N</i> -propylammonium-perruthenate (TPAP)	[EMIM][PF <sub>6</sub> ]/CH <sub>2</sub> Cl <sub>2</sub> or [Et <sub>4</sub> N][Br]/CH <sub>2</sub> Cl <sub>2</sub> <sup>a</sup>	<i>N</i> -methylmorpholine- <i>N</i> -oxide (NMO) or O <sub>2</sub>	[128, 129]
2	RuCl <sub>3</sub> or [RuCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>3</sub> ]	[BMIM][X] <sup>b</sup>		
3	RuCl <sub>3</sub>	[Oct <sub>3</sub> MeN][Cl] or [Me <sub>4</sub> N][OH]	O <sub>2</sub>	[130]
4	[Pd(OAc) <sub>2</sub> ]	[BMIM][BF <sub>4</sub> ], [BMIM][PF <sub>6</sub> ], [BMIM][OOC(CF <sub>3</sub> ) <sub>3</sub> ]	O <sub>2</sub>	[131]
5	[BMIM] <sub>4</sub> [W <sub>10</sub> O <sub>23</sub> ]	[BMIM][BF <sub>4</sub> ]	<i>t</i> -BuOOH	[132]
6	[BMIM] <sub>3</sub> [PO <sub>4</sub> (W(O)(O <sub>2</sub> ) <sub>2</sub> ) <sub>4</sub> ]	[BMIM][Br]	H <sub>2</sub> O <sub>2</sub> (aq)	[133]
7	CuCl + TEMPO	[BMIM][Br]	H <sub>2</sub> O <sub>2</sub> (aq)	[134]
8	[Cu(ClO <sub>4</sub> ) <sub>2</sub> ] + acetamino-TEMPO	[BMIM][PF <sub>6</sub> ]	O <sub>2</sub>	[135]
9	CuCl <sub>2</sub>	[BMPy][PF <sub>6</sub> ]	O <sub>2</sub>	[136]
10	MnO <sub>2</sub>	[BMIM][Cl]/ <i>n</i> -Butanol	O <sub>2</sub>	[137, 138]
11	Mn(salen)-complex	[BMIM][BF <sub>4</sub> ], <sup>c,d</sup> [BMIM][PF <sub>6</sub> ] <sup>c</sup>	aerobic	[139, 140]
		[BMIM][PF <sub>6</sub> ]/CH <sub>2</sub> Cl <sub>2</sub>	PhI(OAc) <sub>2</sub>	[141]

<sup>a</sup> Ref. [128].<sup>b</sup> Ref. [129].<sup>c</sup> Ref. [139].<sup>d</sup> Ref. [140].

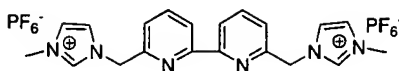
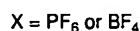
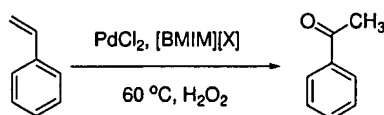


Fig. 5.3-11 Ionic ligand as applied by Wu et al. for the copper catalyzed oxidation of alcohols in [BMIM][PF<sub>6</sub>].



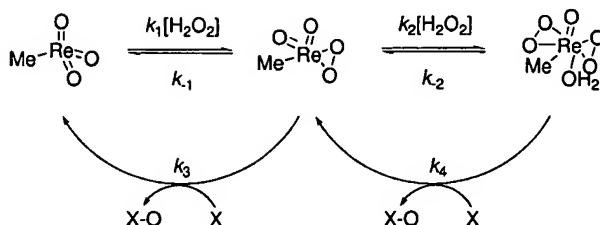
Scheme 5.3-13 The reaction of styrene with H<sub>2</sub>O<sub>2</sub> in the presence of ionic liquids.

to be very sensitive to impurities in the ionic liquid so proper preparation and purification of the ionic medium is necessary [129]. Interesting details concerning the probability of over-oxidation of primary alcohols to acids have been discussed in a number of the published examples (Table 5.3-7, entries 1–3, 7, 8). While it is well known that even traces of water trigger over-oxidation, this consecutive reaction was not found in wet ionic liquids, even addition of water did not lead to significant acid formation. Possibly the strong interaction of the ionic liquid with water makes the latter unavailable for the reaction.

Obviously, all applied ionic liquids were stable against the selected oxidizing agents as no hint of any ionic liquid oxidation is found in the publications. For all these published examples catalyst immobilization and potential recyclability serves as motivation to apply the ionic reaction medium. To improve the immobilization of the catalyst, Wu et al. suggested later a bipyridine ligand carrying two 1-methylimidazolium hexafluorophosphate moieties to be a more appropriate ligand system (Fig. 5.3-11) [142].

The oxidation of alkenes (Wacker oxidation, mainly styrene to acetophenone, Scheme 5.3-13) has been reported to be catalyzed by PdCl<sub>2</sub> in the presence of e.g. [BMIM][PF<sub>6</sub>] [143]. The need for only a small excess (1.15 equiv.) of aqueous H<sub>2</sub>O<sub>2</sub> was demonstrated, which is a significant improvement in H<sub>2</sub>O<sub>2</sub> utilization compared to previously reported methods.

Furthermore thio compounds were oxidized to disulfides with thiols as starting material, using cobalt(II) phthalocyanines in [BMIM][BF<sub>4</sub>] with oxygen [144]. The synthesis of sulfoxides was reported in ionic liquids using thioethers as starting material, a heterogeneous, mesoporous Ti or Ti/Ge catalyst and hydrogen peroxide [145]. Ionic liquids were also applied as reaction and catalyst immobilization media for the Pt(II)-catalyzed oxidation of ketones [146], the iron(III) porphyrin and phosphotungstic acid catalyzed oxidation of oximes [147] as well as for the Baeyer-Villiger oxidation of cyclic ketones [146, 148].



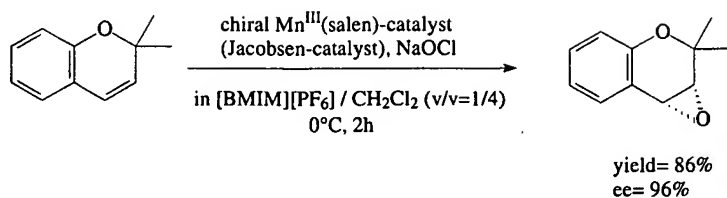
**Scheme 5.3-14** Rhenium oxo- and peroxo-species present in the MTO-UHP epoxidation system in ionic liquids.

Since 2000 several publications dealing with epoxidations and dihydroxylations of olefins have been published. The oxidation of alkenes and allylic alcohols using the urea- $\text{H}_2\text{O}_2$  adduct (UHP) as oxidant and methyltrioxorhenium (MTO) dissolved in  $[\text{EMIM}][\text{BF}_4]$  as catalyst was described by Abu-Omar et al. [149]. Both MTO and UHP dissolve completely in the ionic liquid. Conversions were found to depend on the reactivity of the olefin and the solubility of the olefinic substrate in the reactive layer. In general, the reaction rates of the epoxidation reaction were found to be comparable to those obtained in classical solvents. Spectroscopic investigations showed that both monoperoxo- and diperoxorhenium species were present in the solution and active in the oxidation chemistry (Scheme 5.3-14, see Section 5.3.1.3 for analytic details).

The same system, with  $[\text{BMIM}][\text{BF}_4]$  as the ionic liquid, was applied for the epoxidation of glycols [150]. Here, no attempt was made to isolate the somewhat unstable epoxide and the reaction was conducted in the presence of dibutylphosphate, which gave the glycosyl phosphate product.

Detailed kinetic investigations by Abu-Omar et al. have elucidated the operation of these rhenium oxo- and peroxo-systems in ionic liquids [71b]. First, it was found that the rate of the oxidation by the diperoxorhenium species ( $k_4$ ) is greater than that by the monoperoxorhenium species ( $k_3$ ) for all substrates investigated in all of the ionic liquids applied, whereas in acetonitrile they are approximately the same. For most of the substrates used the  $k_4$  values in  $[\text{EMIM}][\text{BF}_4]$  were similar to those in a 1:1  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  mixture. Investigating different ionic liquids, it was shown that there was no real effect of changing the cation of the ionic liquid, but there was a distinct effect on changing the anion, on both  $k_3$  and  $k_4$ . This was attributed to the greater coordinating ability of the nitrate ion compared to  $[\text{BF}_4]^-$ . The kinetics of the formation of the two peroxo species in ionic liquids ( $k_1$  and  $k_2$ ) have also been studied [151]. The formation of the monoperoxorhenium species was found to be very fast and exact measurement of  $k_1$  was therefore not possible. However,  $k_2$  could be deduced using either UHP or aqueous  $\text{H}_2\text{O}_2$  (30%) as the peroxide source. In pure  $[\text{BMIM}][\text{NO}_3]$   $k_2$  was approximately the same as in acetonitrile, but as water was added the rate constant increased. Several water miscible ionic liquids were compared as 9:1 (v/v) ionic liquid/water solutions and  $k_2$  was found to be the same for both peroxide sources in all of them.

## 408 | 5 Organic Synthesis



**Scheme 5.3-15** Mn-catalyzed asymmetric epoxidation in a [BMIM][PF<sub>6</sub>]/CH<sub>2</sub>Cl<sub>2</sub> (v/v = 1/4) solvent mixture.

Song and Roh investigated the epoxidation of e.g. 2,2-dimethylchromene with a chiral Mn<sup>III</sup>(salen) complex (Jacobsen catalyst) in a mixture of [BMIM][PF<sub>6</sub>] and CH<sub>2</sub>Cl<sub>2</sub> (1:4 v/v) using NaOCl as the oxidant (Scheme 5.3-15) [152].

Even if the reaction medium consisted mainly of CH<sub>2</sub>Cl<sub>2</sub> the authors described a clear enhancement of the catalyst activity by the addition of the ionic liquid. In the presence of the ionic liquid a 86% conversion of 2,2-dimethylchromene was observed after 2 h. Without the ionic liquid the same conversion was only obtained after 6 h. In both cases the enantiomeric excess was as high as 96%. Moreover, the ionic catalyst solution could be reused several times after product extraction. However, after five recycles, the conversion dropped from 83% to 53%, which was explained, according to the authors, by a slow degradation process of the Mn<sup>III</sup> complex.

For non-activated olefins like styrol, cyclohexene and cyclooctene Chauhan et al. investigated iron(III)porphyrine systems in combination with H<sub>2</sub>O<sub>2</sub> as a suitable epoxidation system [153]. The metalloporphyrines were used as model catalysts for cytochrome P450 and were immobilized in [BMIM]Br. The yields were found to depend on the applied olefin and varied from 42% for cyclohexene, 74% for styrene, to 81% for cyclooctene. Recycling was possible for the epoxidation of styrene in 5 runs under biphasic reaction conditions and the yield decreased from 74% for the first run to 62% for the fifth run.

For the oxidation of alkanes Li et al. used iodobenzene diacetate [PhI(OAc)<sub>2</sub>] as oxygen source. An electron-deficient manganeseporphyrin catalyst was immobilized in [BMIM][PF<sub>6</sub>] and tested in liquid-liquid biphasic reaction mode with CH<sub>2</sub>Cl<sub>2</sub> as organic phase [154]. They found the catalyst more active in the [BMIM][PF<sub>6</sub>]/CH<sub>2</sub>Cl<sub>2</sub> system than in neat CH<sub>2</sub>Cl<sub>2</sub>. The increase in activity was attributed by them to the higher polarity of the ionic liquid.

As a further oxygen source *tert*-butyl hydroperoxide (TBHP) was applied in combination with dioxomolybdenum(VI) complexes immobilized in ionic liquid for the epoxidation of *cis*-cyclooctene [155]. Again, a strong dependence of reactivity, selectivity and the ability for recycling conditions on the chosen ionic liquid and solvent was described.

Finally, it should be mentioned that Yamaguchi et al. used the SILP concept to immobilize an oxidation catalyst [156]. They found that peroxotungstate [ $\{W(=O)(O_2)_2(H_2O)\}_2(\mu-O)\}^{2-}$ ] can be immobilized on a dihydroimidazolium-based ionic liquid-modified SiO<sub>2</sub> surface to get an efficient heterogeneous

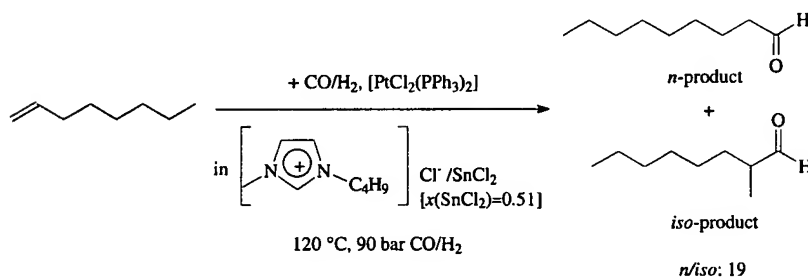
epoxidation system with  $\text{H}_2\text{O}_2$  as oxidant. The system showed the same activity as the corresponding homogeneous analogue. The catalyst was reused three times without any loss in catalytic activity and selectivity (99% yield, >99% selectivity). More details about catalytic SILP systems are to be found in Section 5.6.

### 5.3.2.3 Hydroformylation

In hydroformylation, biphasic catalysis is a well-established method for effective catalyst separation and recycling. In the case of Rh-catalyzed hydroformylation reactions this principle is technically realized in the Ruhrchemie-Rhône-Poulenc-process, where water is used as the catalyst phase [157]. Unfortunately, this process is limited to  $\text{C}_2$ – $\text{C}_5$ -olefins due to the low water solubility of higher olefins. Nevertheless, the hydroformylation of many higher olefins is of commercial interest. One example is the hydroformylation of 1-octene for the selective synthesis of linear nonanal. The latter can be obtained in high selectivity by application of special ligand systems around the catalytic center. However, the additional costs related to these ligands make it even more economically attractive to develop new methods for an efficient catalyst separation and recycling. In this context, biphasic catalysis using an ionic liquid as catalyst layer is a highly promising approach.

As early as 1972 Parshall described the platinum-catalyzed hydroformylation of ethene in tetraethylammonium trichlorostannate melts,  $[\text{NEt}_4][\text{SnCl}_3]$  [1]. The ionic liquid used for these investigations has a melting point of  $78^\circ\text{C}$ . Later, the platinum-catalyzed hydroformylation in the chlorostannate room-temperature ionic liquid  $[\text{BMIM}]\text{Cl}/\text{SnCl}_2$  was studied in the author's group anew. The hydroformylation of 1-octene was carried out with remarkable *n*/*iso*-selectivities (Scheme 5.3-16) [158].

Despite the limited solubility of 1-octene in the ionic catalyst phase, a remarkable activity of the platinum catalyst was achieved (turnover frequency (TOF) =  $126\text{ h}^{-1}$ ). However, the system has to be carefully optimized to avoid significant formation of hydrogenated by-product. Detailed studies to identify the best reaction conditions revealed that in the chlorostannate ionic liquid  $[\text{BMIM}]\text{Cl}/\text{SnCl}_2$  [ $x(\text{SnCl}_2) = 0.55$ ] the highest ratio of hydroformylation to hydrogenation is found at high syngas pressure and low temperature. At  $80^\circ\text{C}$  and 90 bar  $\text{CO}/\text{H}_2$  pressure more than



**Scheme 5.3-16** Biphasic, Pt-catalyzed hydroformylation of 1-octene using a slightly acidic  $[\text{BMIM}]\text{Cl}/\text{SnCl}_2$  ionic liquid as catalyst layer.

90% of all products are n-nonanal and iso-nonanal, the ratio between these two hydroformylation products being as high as 98.6:1.4 (n/iso = 70.4) [158].

Moreover, these experiments revealed some unique properties of the chlorostannate ionic liquids. In contrast to other known ionic liquids, the chlorostannate system combines a certain Lewis-acidity with high compatibility to functional groups. The first led, in the hydroformylation of 1-octene, to the activation of  $(PPh_3)_2PtCl_2$  by a Lewis acid–base reaction with the acidic ionic liquid medium. The high compatibility to functional groups is demonstrated by the catalytic reaction in the presence of CO and hydroformylation products.

Later, van Eldik et al. studied in more detail the kinetics of the formation of the active hydroformylation catalysts  $cis-[Pt(PPh_3)_2Cl(SnCl_3)]$  and  $cis-[Pt(PPh_3)_2(SnCl_3)_2]$  from the precursor  $cis-[Pt(PPh_3)_2Cl_2]$  in the presence of  $SnCl_2$  in different imidazolium-based chlorostannate ionic liquids (for analytic details see Section 5.3.1.3) [73].

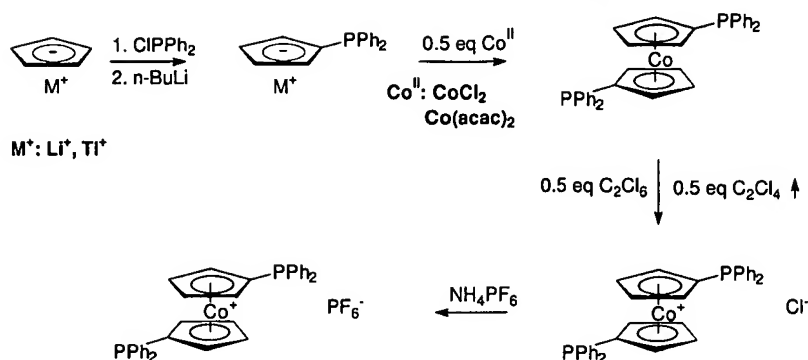
Ruthenium- and cobalt-catalyzed hydroformylation of internal and terminal alkenes in molten  $[PbU_4]Br$  was reported by Knifton as early as 1987 [2]. He described a stabilization of the active ruthenium-carbonyl complex by the ionic medium. An increased catalyst lifetime at low synthesis gas pressures and higher temperatures was observed.

First investigations of the rhodium-catalyzed hydroformylation in room-temperature liquid molten salts were published by Chauvin et al. in 1995 [6, 159]. The hydroformylation of 1-pentene with the neutral catalyst system  $[Rh(CO)_2(acac)]/triarylphosphine$  was carried out in a biphasic reaction using  $[BMIM][PF_6]$  as the ionic liquid. However, with none of the ligands tested was it possible to combine high activity, complete retention of the catalyst in the ionic liquid and high selectivity for the desired linear hydroformylation product at this time. The use of  $PPh_3$  resulted in significant leaching of the Rh catalyst out of the ionic liquid layer. In this case, the catalyst is active in both phases, which makes a clear interpretation of solvent effects on the reactivity difficult. The catalyst leaching could be suppressed by the application of sulfonated triaryl phosphine ligands, but a major decrease in catalytic activity was found with these ligands ( $TOF = 59\ h^{-1}$  with  $tppm$ s compared to  $333\ h^{-1}$  with  $PPh_3$ ). Moreover, all of the ligands used in Chauvin's work showed poor selectivity to the desired linear hydroformylation product (n/iso-ratio between 2 and 4). Obviously, the Rh-catalyzed, biphasic hydroformylation of higher olefins in ionic liquids requires the use of ligand systems that are specifically designed for this application. Thus, these early results stimulated the research for other immobilizing, ionic ligand systems that provide good catalyst immobilization without deactivation of the catalyst.

#### **Ligand optimization studies for hydroformylation in ionic liquids**

A first ligand system especially designed for the use in ionic liquids was described in 2000 by Salzer et al. [160]. Cationic ligands with a cobaltocenium backbone were successfully used in the biphasic, Rh-catalyzed hydroformylation of 1-octene. 1,1'-Bis(diphenylphosphino)cobaltocenium hexafluorophosphate (cdpp) proved to





**Scheme 5.3-17** Synthesis of 1,1'-Bis(diphenylphosphino)cobaltocenium hexafluorophosphate.

be an especially promising ligand. The compound can be synthesized according to Scheme 5.3-17 by mild oxidation of 1,1'-bis(diphenylphosphino)cobaltocene with  $C_2Cl_6$  and anion exchange with  $[NH_4][PF_6]$  in acetone. (for detailed ligand synthesis see Ref. [160]).

The results obtained in the biphasic hydroformylation of 1-octene are presented in Table 5.3-8. In order to evaluate the properties of the ionic diphosphine ligand with a cobaltocenium backbone, the results with the cdpp ligand are compared with those obtained with  $PPh_3$ , two common neutral bidentate ligands and with Natppts as a standard anionic ligand [160].

It is noteworthy that a clear enhancement of the selectivity to the linear hydroformylation product is observed only with cdpp (Table 5.3-8, entry e). With all other ligands, the *n*/*iso*-ratios are in the range 2 to 4. While this is in accordance with known results in the case of  $PPh_3$  (entry a) and dppe (entry c) (in comparison to the monophasic hydroformylation [161]) and also with reported results in the case of

**Table 5.3-8** Comparison of different phosphine ligands in the Rh-catalyzed hydroformylation of 1-octene in  $[BMIM][PF_6]$ .

Entry	Ligand	TOF/ $h^{-1}$	<i>n</i> / <i>iso</i>	<i>S</i> ( <i>n</i> -ald) <sup>a</sup> (%)
a	$PPh_3$	426	2.6	72
b	tppts	98	2.6	72
c	dppe	35	3.0	75
d	dppf	828	3.8	79
e	cdpp	810	16.2	94

Conditions: ligand/Rh: 2:1,  $CO/H_2 = 1:1$ ,  $t = 1$  h,  $T = 100$  °C,  $p = 10$  bar, 1-octene/Rh = 1000, 5 mL  $[BMIM][PF_6]$ ; dppe: bis(diphenylphosphinoethane); dppf: 1,1'-bis(diphenylphosphino)ferrocene.

<sup>a</sup>*S* (*n*-ald) = selectivity to *n*-nonanal in the product.

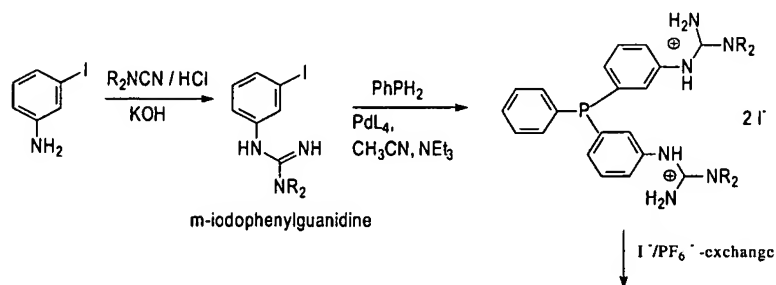
Natppts (entry b; in comparison to the biphasic hydroformylation of 1-pentene in [BMIM][PF<sub>6</sub>] [6]), it is more remarkable for the bidentate metallocene ligand dppf.

Taking into account the high structural similarity of dppf and cdpp, their different influence on the reaction's selectivity has to be attributed to electronic effects. The electron density at the phosphorus atoms is significantly lower in the case of cdpp due to the electron-withdrawing effect of the formal cobalt(III) central atom in the ligand. This interpretation is supported by former work from Casey et al. [162] and Duwell et al. [163]. These groups described positive effects of ligands with electron-poor phosphorus atoms in selective hydroformylation reactions, which they attribute to their ability to allow back-bonding from the catalytically active metal atom. It has to be pointed out that with the phosphinocobaltocenium ligand cdpp the reaction takes place almost exclusively in the ionic liquid phase (almost clear and colorless organic layer, less than 0.5% Rh in the organic layer). An easy catalyst separation by decantation was possible. Moreover, it was found that the recovered ionic catalyst solution could be reused at least one more time with the same activity and selectivity as in the original run [160].

Cationic phosphine ligands containing guanidiniumphenyl moieties were originally developed to make use of their pronounced solubility in water [164, 165]. They were shown to form active catalytic systems in Pd mediated C–C coupling reactions between aryl iodides and alkynes (Castro-Stephens-Sonogashira reaction) [166] and Rh catalyzed hydroformylation of olefins in aqueous two-phase systems [167].

The modification of neutral phosphine ligands with cationic phenylguanidinium groups proved to be a very powerful tool to immobilize Rh-complexes in ionic liquids such as e.g. [BMIM][PF<sub>6</sub>] [168]. The guanidinium-modified triphenylphosphine ligand was prepared according to Scheme 5.3-18 by anion exchange with [NH<sub>4</sub>][PF<sub>6</sub>] in aqueous solution from the corresponding iodide salt. The latter can be prepared as previously described by Stelzer et al. [165].

In contrast to the use of PPh<sub>3</sub> as the ligand, the reaction takes place solely in the ionic liquid layer when the guanidinium-modified triphenylphosphine is applied. In the first catalytic run the hydroformylation activity was found to be somewhat lower than with PPh<sub>3</sub> (probably due to the fact that some of the activity observed with PPh<sub>3</sub>



Scheme 5.3-18 Synthesis of a guanidinium-modified triphenylphosphine ligand.

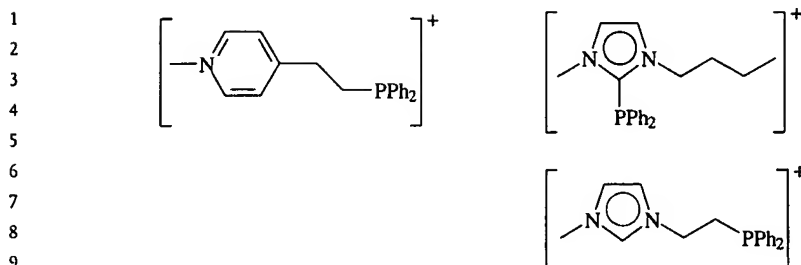


Fig. 5.3-12 Cationic diphenylphosphine ligands as used in the biphasic, Rh-catalyzed hydroformylation of 1-octene in e.g. [BMIM][PF<sub>6</sub>].

takes place in the organic layer). However, due to the excellent immobilization of the Rh catalyst with the guanidinium modified ligand [leaching is <0.07% per run according to ICP analysis (detection limit)], the catalytic activity does not drop over the first ten recycling runs. For the recycling runs the organic layer was decanted after each run (under normal atmosphere) and the ionic catalyst layer remained in the autoclave for the next hydroformylation experiment. Already after five recycling runs, the overall catalytic activity obtained with the ionic catalyst solution containing the guanidinium-modified ligand is higher than can be realized with the simple PPh<sub>3</sub> ligand. With both ligands the *n*/*iso*-ratio of the hydroformylation products is in the expected range of 1.7–2.8.

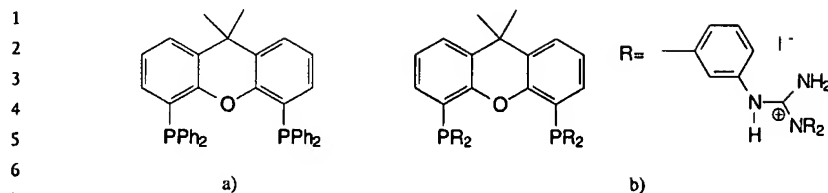
Alternative methods to immobilize monodentate phosphine ligands by attaching them to ionic groups with high similarity to the ionic liquid's cation have also been reported. Both pyridinium-modified phosphine ligands [169] and imidazolium-modified phosphine ligands [170, 171] have been synthesized and applied in Rh-catalyzed hydroformylation (see Fig. 5.3-12). While the presence of the ionic group led to better immobilization of the Rh catalyst in the ionic liquid in all cases no outstanding reactivity or selectivity were observed with these ligands. This is not really surprising since all these ligands are electronically and sterically closely related to PPh<sub>3</sub>.

Further development was aimed at adopting this immobilization concept to a ligand structure that promises better regioselectivity in the hydroformylation reaction. It is well-known that bidentate phosphine ligands with large P–metal–P bite angles form highly regioselective hydroformylation catalysts [172]. Here, xanthene type ligands (P–metal–P ~ 110°) developed by van Leeuwen's group proved to be especially suitable allowing, for example, an overall selectivity of 98% towards the desired linear aldehyde in 1-octene hydroformylation [173, 174].

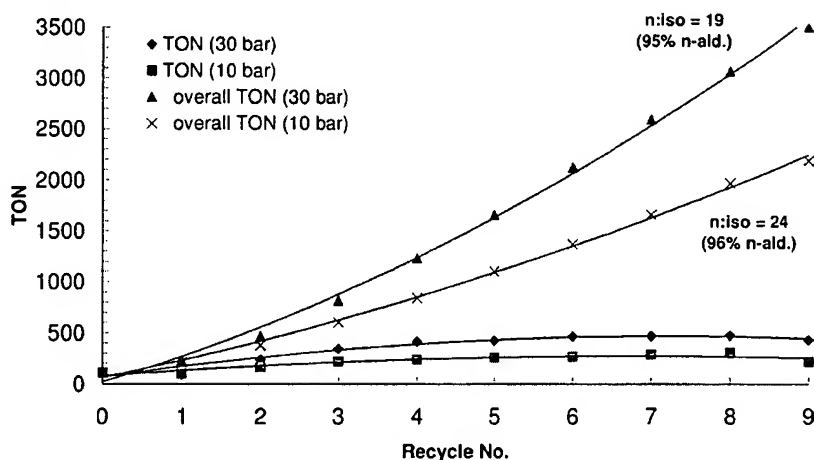
While unmodified xanthene ligands (Fig. 5.3-13(a)) show highly preferential solubility in the organic phase in the biphasic mixture 1-octene/[BMIM][PF<sub>6</sub>], even at room temperature, the application of the guanidinium-modified xanthene ligand (Fig. 5.3-13(b)) resulted in excellent immobilization of the Rh catalyst in the ionic liquid.

The guanidinium-modified ligand is synthesized by reacting the xanthenediphosphine [175] with iodophenylguanidine in a Pd(0)-catalyzed coupling reaction. The

## 414 | 5 Organic Synthesis



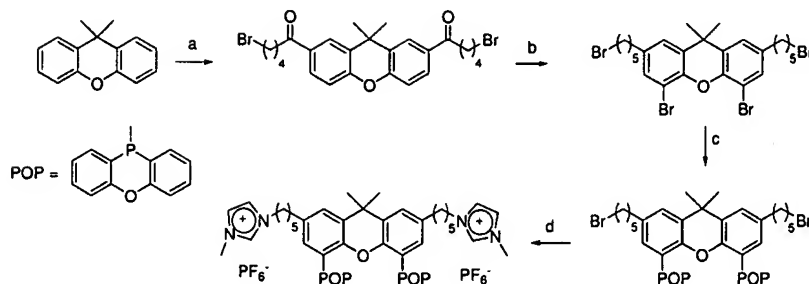
8 **Fig. 5.3-13** Unmodified (a) and guanidinium-modified xanthene ligand  
9 (b) as used in the biphasic, Rh-catalyzed hydroformylation of 1-octene.



27 **Fig. 5.3-14** Recycling experiments – Rh-catalyzed, biphasic 1-octene  
28 hydroformylation in [BMIM][PF<sub>6</sub>] using a guanidinium-modified  
29 diphosphine ligand with a xanthene backbone.

30  
31 ligand was tested in the Rh-catalyzed hydroformylation in ten consecutive recycling  
32 runs. The results are presented in Fig. 5.3-14. It is noteworthy that the catalytic  
33 activity increases during the first runs, achieving a stable level only after the fourth  
34 recycling run. This behavior is attributed to a certain catalyst pre-forming time but  
35 also to impurities of iodoaromate in the ligand used. Probably, these are slowly  
36 washed out of the catalyst layer during the first catalytic runs.

37 After ten consecutive runs the overall turnover number reached 3500 mol 1-  
38 octene converted/mol Rh-catalyst. In agreement with these recycling experiments,  
39 no Rh could be detected in the product layer by AAS or ICP, indicating a leaching  
40 of less than 0.07%. In all experiments very good selectivities for the linear aldehyde  
41 were obtained, thus proving that the attachment of the guanidinium moiety to the  
42 xanthene backbone does not influence its known positive effect on the regioselectivity  
43 of the reaction. Thus, these results demonstrate that the modification of known  
44 phosphine ligands with guanidinium groups is a simple and very efficient method  
45 to fully immobilize transition metal complexes in ionic liquids.



**Scheme 5.3-19** Synthesis of a dicationic phenoxaphosphino-modified xantphos type ligand as used in the hydroformylation of 1-octene in [BMIM][PF<sub>6</sub>].

An imidazolium-based dicationic phenoxaphosphino-modified xantphos type ligand was applied by van Leeuwen et al. for the hydroformylation of 1-octene in [BMIM][PF<sub>6</sub>] [176]. The ligand was prepared in a six-step synthesis according to Scheme 5.3-19.

The ligand provided excellent immobilization of the catalyst system with no Rh or P leaching detectable in the organic product phase and no loss in catalyst activity or selectivity observable in seven recycling experiments. In contrast, a catalyst preformation period was observed during the first four cycles, after which the catalyst activity reached a constant TOF level of 110 h<sup>-1</sup>. Additionally, the ionic catalyst solution was found to be pretty robust as it could be stored under air for more than 14 days without loss of activity. This study was extended recently by the same group still using dicationic phenoxaphosphino-modified xantphos ligands for the Rh-catalyzed hydroformylation of 1-octene in [BMIM][PF<sub>6</sub>] [177]. They carried out detailed investigations on stirring speed and catalyst concentration variation. When lowering the rhodium concentration from 6.4 mmol l<sup>-1</sup> to 1.7 mmol l<sup>-1</sup> a dramatic increase in the TOF together with a slight increase in regioselectivity was observed with TOFs up to 7400 h<sup>-1</sup> and product ratios n-nonanal/iso-nonanal as high as 64 being reported. The results indicated that the overall reaction rate of the system was still influenced by mass transport issues, even at a stirring rate of 1600 min<sup>-1</sup>.

Apart from charged phosphine ligands, phosphite ligands have also been explored in ionic liquids. Since phosphite ligands are usually unstable in aqueous media this adds, apart from the much better solubility of higher olefins in ionic liquids, another important advantage to biphasic hydroformylation using ionic liquids in comparison to the, well-known, biphasic reaction in water. The group of Olivier-Bourbigou has shown, for example, that phosphite ligands can be used in the Rh-catalyzed hydroformylation of 1-hexene in various imidazolium and pyrrolidinium ionic liquids with better selectivity to linear aldehyde compared to the well-known phosphine systems [169]. An earlier study by Keim et al. used a bulky phosphite ligand to promote the selective Rh-catalyzed hydroformylation of methyl-3-pentenoate in [BMIM][PF<sub>6</sub>] [30].

### 1 Ionic liquid optimization studies for hydroformylation in ionic liquids

2 Apart from all these attempts to improve the immobilization of the phosphine  
3 ligands in the ionic medium, other research activities were directed to optimize  
4 the structure of the ionic liquid medium for specific hydroformylation applications.  
5 Olivier-Bourbigou and coworkers investigated the hydroformylation of 1-hexene  
6 in a variety of ionic liquids with imidazolium and pyrrolidinium cations and a  
7 range of different anions [169]. Applying  $[\text{Rh}(\text{CO})_2(\text{acac})]$  with four equivalents of  
8 the charged phosphine TPPMS as the catalyst system they measured the turnover  
9 frequency of the catalyst in the different ionic liquids and found for different  $[\text{BF}_4]^-$ ,  
10  $[\text{PF}_6]^-$ ,  $[\text{CF}_3\text{SO}_3]^-$ ,  $[\text{CF}_3\text{CO}_2]^-$  melts the TOFs to be dependent on the solubility of  
11 the 1-hexene in the respective ionic liquid.

12 An important step towards the technical applicability of ionic liquids in industrial  
13 hydroformylation is the successful replacement of hexafluorophosphate (and other  
14 halogen-containing) ionic liquids by some cheap and halogen-free ionic liquids. Rh-  
15 catalyzed hydroformylation offers a specific potential in this respect as the reaction  
16 is not too sensitive to slightly coordinating anions such as alkyl- and aryl sulfonates  
17 and alkylsulfates. The first practical attempts were made by Andersen et al. [13].  
18 They investigated the Rh-catalyzed hydroformylation of 1-hexene in high melting  
19 phosphonium tosylate salts, such as butyltriphenylphosphonium tosylate (mp =  
20 116–117 °C). Obviously, the high melting point of the salts used makes the process-  
21 ing of the reaction difficult, even if the authors describe easy product isolation by  
22 pouring the product off the solid catalyst medium at room temperature.

23 Later, Wasserscheid et al. introduced much lower melting 1,3-dialkylimidazolium  
24 benzenesulfonate, tosylate and octylsulfate ionic liquids to biphasic, Rh-catalyzed  
25 hydroformylation of 1-octene [15]. The catalyst activity obtained with these systems  
26 was in all cases equal or even higher than that with the commonly used  $[\text{BMIM}][\text{PF}_6]$ .  
27 Taking into account the much lower costs of the ionic medium, the better hydrolysis  
28 stability and the wider disposal options related to, for example, an octylsulfate ionic  
29 liquid in comparison to  $[\text{BMIM}][\text{PF}_6]$ , the technical relevance of this anion switch  
30 is very obvious.

31 In order to eliminate the possibility for *in situ* carbene formation Raubenheimer  
32 et al. synthesized 1-alkyl-2,3-dimethylimidazolium triflate ionic liquids and applied  
33 these as solvents in the rhodium catalyzed hydroformylation of 1-hexene and 1-  
34 dodecene [178]. Both, the classical Wilkinson type complex  $[\text{RhCl}(\text{TPP})_3]$  and the  
35 chiral, stereochemically pure complex  $(-)-(\eta^4\text{-cycloocta-1,5-diene})\text{-}(2\text{-menthyl-4,7-}$   
36  $\text{dimethylindenyl})\text{rhodium(I)}$  were applied. The Wilkinson catalyst showed low se-  
37 lectivity towards n-aldehydes whereas the chiral catalyst formed branched aldehydes  
38 predominantly. Hydrogenation was significant with up to 44% alkanes being formed  
39 and also a significant activity for olefin isomerization was observed. Additionally,  
40 hydroformylation was found to be slower in the ionic liquid than in toluene. Some of  
41 the findings were attributed by the authors to the lower gas solubility in the ionic li-  
42 quid and the slower diffusion of the reactive gases  $\text{H}_2$  and CO into the ionic medium.

43 Highly viscous triazine-based ionic liquids have been recently applied for the  
44 rhodium catalyzed hydroformylation of 1-octene [179]. Hydroformylation was  
45 carried out at 69 bar syngas pressure and total 1-octene conversion was achieved

1 within 14 to 19 h. Only the two isomers n-nonanal and 2-methyloctanal were  
2 obtained as products and no hydrogenation or isomerization of the feedstock was  
3 reported. The catalyst was shown to be recyclable in principle with only slight  
4 decrease in activity and selectivity over two cycles. Rh leaching was determined by  
5 ICP to be between 0.40 and 26.5 ppm.

6 The hydroformylation of 1-tetradecene in novel ionic liquids consisting of am-  
7 monium salts with polyether-tail has been reported by Jin et al. [180]. The highly  
8 viscous salts were synthesized by protonation of a polyether-tailored amine with p-  
9 toluenesulfonic acid. The Rh-catalyzed hydroformylation reactions were carried out  
10 at 105 °C and 50 bar syngas pressure in a biphasic system using heptane as extraction  
11 phase. Severe Rh leaching was observed when using TPP as ligand, similar to results  
12 reported earlier by Chauvin [6b]. The ligands TPPTS and octylpolyethyleneglycol-  
13 phenyl-phosphite were applied in order to achieve better immobilization of the Rh  
14 in the ionic liquid phase. The Rh leaching could be suppressed in this way without  
15 loss of activity. However, the selectivity to the linear pentadecanal was extremely  
16 low in all cases with only 17 and 19% of the desired product being formed.

#### 17 18 19 *Process related studies*

20 Process related studies of transition metal catalyzed hydroformylation in ionic liq-  
21 uids mainly focused on a better utilization of the amount of ionic liquid and thus  
22 on a reduction of the amount of ionic liquids required. A key aspect in this context  
23 is to enhance the solubility of the reactants CO, H<sub>2</sub> and olefin in the ionic liquid  
24 and to enhance the mass transfer between the gas phase/organic fluid and the ionic  
25 liquid phase.

26 The solubilities of H<sub>2</sub> [181] and CO [182] in many different ionic liquids have  
27 been measured in this context by Dyson and coworkers using high-pressure <sup>1</sup>H-  
28 or <sup>13</sup>C-NMR spectroscopy. CO solubility at ambient conditions were found to be  
29 in the range 8.05–0.67 × 10<sup>2</sup> MPa<sup>2</sup> which were in the same range than those  
30 measured for H<sub>2</sub> in the same ionic liquids (about 6.6–0.7 × 10<sup>2</sup> MPa). In order to  
31 establish the effect of the CO solubility on the rate of hydroformylation reactions,  
32 the same authors studied the [RhH(CO)(PPh<sub>3</sub>)<sub>3</sub>] catalyzed hydroformylation of  
33 5-hexen-2-one comparing catalyst activities in the different ionic liquids with the  
34 determined gas solubilities.

35 As expected from the known kinetics of hydroformylation the authors found  
36 that increasing hydrogen solubility in the ionic liquid (either induced by increased  
37 hydrogen pressure or by higher hydrogen solubility) increased the reaction rate  
38 while higher CO concentration slowed the hydroformylation down.

39 A well established way in multiphasic catalysis to improve the substrate solubility  
40 in the catalyst phase is the addition of appropriate co-solvents. This approach  
41 has been studied for the hydroformylation of 1-octene with a [Rh(CO)<sub>2</sub>(acac)]-  
42 (sulfoxantphos) catalyst system in [BMIM][PF<sub>6</sub>] by Dupont et al. [183]. They

43  
44  
45 <sup>2</sup> Henry's constant,  $K_H =$ .

found that the selectivity to n-nonanal was best in pure [BMIM][PF<sub>6</sub>] compared to the same ionic liquid with e.g. added co-solvent toluene. They reported catalyst activities which were very similar for the reaction in the pure ionic liquid and the ionic liquid/toluene system.

Another interesting development to improve the processibility of the Rh-catalyzed hydroformylation reaction in ionic liquids is to work in the presence of supercritical CO<sub>2</sub> as extraction phase. The use of scCO<sub>2</sub> as the mobile phase in such a continuous multiphasic operation brings along a number of very attractive features such as very elegant product removal from the catalyst phase, reduction of the ionic liquid's melting point [184] and viscosity [185] (and thus diffusion rate [186]). Most important for the hydroformylation application may be the fact that the relatively large amount of CO<sub>2</sub> that dissolves in the ionic liquid (see Section 3.3. for details) acts as a very powerful cosolvent to increase hydrogen solubility in the ionic liquid [187]. The continuous hydroformylation of 1-octene in the biphasic system [BMIM][PF<sub>6</sub>]/scCO<sub>2</sub> has been studied in detail by Cole-Hamilton et al. [188, 189]. Together with other examples of transition metal catalysis in ionic liquid/scCO<sub>2</sub> systems this specific example will be described in detail in Section 5.7.

Finally, SILP catalysis has been introduced in the last three years using mainly hydroformylation as the model reaction to develop the technology [190]. Due to the general importance of SILP catalysis a separate section is devoted to this topic (see Section 5.6) in which all details of the studied SILP-hydroformylation systems can be found.

#### 5.3.2.4 Heck Reaction and Other Pd-catalyzed C–C-coupling Reactions

##### *Early studies and reactions in [NBu<sub>4</sub>]Br*

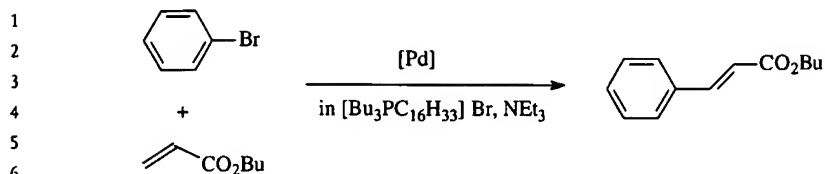
The Heck reaction and other related transformations for selective C–C-couplings are receiving a great deal of attention among synthetic chemists, due to their versatility for fine chemical synthesis. However, these reactions suffer, in many cases, from the instability of the Pd catalysts used, leading to high catalyst consumption and difficult processing. In recent years, many different versions of the Heck reaction have been developed using ionic liquids as the reaction medium and these have already been extensively reviewed from different perspectives [191].

The use of ionic liquids as reaction media for the palladium-catalyzed Heck reaction was first described by Kaufmann et al. in 1996 [192]. The reaction of bromobenzene with acrylic acid butyl ester to *trans*-cinnamic acid butyl ester succeeded in high yield in molten tetraalkylammonium and tetraalkylphosphonium bromide salts, without addition of phosphine ligands (Scheme 5.3-20).

The authors describe a stabilizing effect of the ionic liquid on the palladium catalyst. In almost all reactions no precipitation of elemental palladium was observed, even at complete conversion of the aromatic halide. The reaction products were isolated by distillation from the non-volatile ionic liquid.

Extensive studies of the Heck reaction in low melting salts have been presented by Hermann and Böhm [193]. Their results indicate that the application of ionic solvents show clear advantages in comparison to commonly used organic solvents (e.g., DMF), especially for the conversion of the commercially interesting chloroarenes.

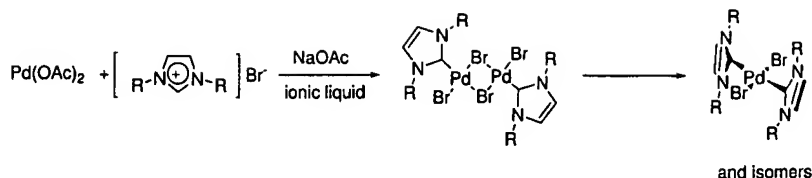




8 **Scheme 5.3-20** Pd-catalyzed Heck reaction of acrylic acid butyl ester  
9 with bromobenzene carried out in a phosphonium bromide salt.

10  
11 With almost all catalyst systems tested an additional activation and stabilization was  
12 observed. Molten  $[\text{NBu}_4]\text{Br}$  (mp = 103 °C) proved to be a specially suitable reaction  
13 medium among the ionic solvent systems investigated. In the reaction of bromoben-  
14 zene with styrene using diiodo-bis(1,3-dimethylimidazolin-2-ylidene)-palladium(II)  
15 as catalyst the yield of stilbene could be increased from 20% (DMF) to over 99%  
16 ( $[\text{NBu}_4]\text{Br}$ ) under otherwise identical conditions. Again, a distillative product sepa-  
17 ration from the non-volatile ionic catalyst solution was possible. The latter could be  
18 re-used up to 13 times without significant drop in activity. Additional advantages of  
19 the new solvent concept arise from the excellent solubility of all reacting molecules  
20 in the ionic solvent and the possibility of using cheap inorganic bases.

21 This work was followed up by other research groups using different substrates  
22 and other Pd-precursor/ligand combinations in molten  $[\text{NBu}_4]\text{Br}$  for Heck cou-  
23 pling. Muzart et al. described the coupling of aryl iodides and bromides with allylic  
24 alcohols to the corresponding  $\beta$ -arylated carbonyl compounds [194]. Calò et al. re-  
25 ported the Heck coupling of substituted acrylates with bromobenzene catalyzed  
26 by Pd-benzothiazole carbene complexes in molten  $[\text{NBu}_4]\text{Br}$  [195]. The same sol-  
27 vent was found to be essential in investigations carried out by Buchmeiser et al.  
28 aiming for the Pd-catalyzed Heck coupling of aryl chlorides and for the amination  
29 of aryl bromides [196]. Later, Handy and coworkers demonstrated that the addi-  
30 tion of tetrabutylammonium salts to a  $[\text{BMIM}][\text{BF}_4]$  also had a beneficial effect for  
31 the reaction of methyl acrylate with iodobenzene. Depending on the anion of the  
32 tetrabutylammonium salt, the yield was improved from 53% (no additional salt)  
33 to 96% ( $[\text{Bu}_4\text{N}]\text{Br}$ ), 90% ( $[\text{Bu}_4\text{N}]\text{Cl}$ ), and 89% ( $[\text{Bu}_4\text{N}]\text{I}$ ) respectively [197]. Similar  
34 findings were earlier described by Jeffery for Heck reactions in a strictly anhydrous  
35 organic medium, in a water–organic solvent mixture or in water alone, where it  
36 was believed that the salts were acting as phase-transfer catalysts [198]. Zou et al.  
37 reported Heck reactions of aryl halides with butyl acrylate and Suzuki reaction  
38 of *p*-tolylboronic acid with iodobenzene in high-melting-point  $[\text{Bu}_4\text{N}][\text{BF}_4]$ , *N,N*-  
39 dialkylpyrrolidiniums and *N,N*-dialkylpiperidiniums melts with additional water or  
40 toluene to form biphasic mixtures [199]. They found a significant melting point  
41 suppression of the ionic liquid caused by water or toluene. In this way a ligand-less  
42 biphasic reaction system using  $\text{PdCl}_2$  as catalyst could be realized at 90 °C. While one  
43 of the obvious objectives of the use of ionic liquids in Heck reactions is to increase  
44 the solubility of the organic starting materials in the catalyst solution, the ability to  
45 generate stable Heck catalysts without ligand addition suggests that the ionic liquid



**Scheme 5.3-21** The formation of  $[\text{PdBr}_2(\text{BMimy})_2]$  in  $[\text{BMIM}]\text{Br}$ .

environment acts as a catalyst stabilizing medium in the system. Tetraalkylammonium salts have also been used to stabilize nanoparticles/colloids when used as a solute in molecular solvents [200]. It was suggested by Herrmann that such effects may also play a role when  $[\text{Bu}_4\text{N}]\text{Br}$  was used as the ionic liquid [201].

#### **In situ carbene complex and Pd nanoparticle formation**

*N*-heterocyclic carbene (NHC) ligands have been used in volatile organic solvents to prepare catalysts for a wide variety of reactions, many palladium catalyzed [202]. The use of imidazolium-based ionic liquids in the Pd-catalyzed Heck reaction always carries the possibility of an *in situ* formation of Pd–carbene complexes (for more details see Section 5.3.1.2). The formation of the latter under the reaction conditions of the Heck reaction was confirmed by the investigations of Xiao et al. [49]. They described a significantly enhanced reactivity of the Heck reaction in  $[\text{BMIM}]\text{Br}$  in comparison to the same reaction in  $[\text{BMIM}][\text{BF}_4]$  and explained this difference with the fact that only in the bromide melt was the formation of Pd–carbene complexes observed. While ‘palladium black’ was observed to precipitate during reactions performed in  $[\text{BMIM}][\text{BF}_4]$ , Xiao et al. could isolate the complexes  $[\text{PdBr}_2(\text{BMimy})_2]$  and  $[\text{Pd}_2(\mu\text{-Br})_2\text{Br}_2(\text{BMimy})_2]$  (BMimy = 1-butyl-3-methylimidazolylidene) from the  $[\text{BMIM}]\text{Br}$  solution (see Scheme 5.3-21). Synthesis of Pd-imidazolylidene complexes from imidazolium halide and  $\text{Pd}(\text{OAc})_2$  has been reported to proceed particularly easily [203].

However, when the authors dissolved independently prepared  $[\text{PdBr}_2(\text{BMimy})_2]$  in  $[\text{BMIM}][\text{BF}_4]$  the yield of the reaction was the same as that when palladium acetate was used. This suggests that, if the  $[\text{PdBr}_2(\text{BMimy})_2]$  complex is responsible for the improved yields in  $[\text{BMIM}]\text{Br}$ , it must rapidly transform in  $[\text{BMIM}][\text{BF}_4]$ .

Indication for a possible transformation pathway was given by an EXAFS study of palladium acetate dissolved in  $[\text{BMIM}][\text{BF}_4]$ ,  $[\text{BMIM}][\text{PF}_6]$ ,  $[\text{BPy}][\text{BF}_4]$  and  $[\text{BPy}][\text{PF}_6]$  showing that a gradual change to palladium metal occurred [204]. In contrast, the use of  $[\text{HMIM}]\text{Cl}$  led to the formation of  $[\text{PdCl}_2(\text{HMimy})_2]$  which is entirely consistent with Xiao’s observations above [49]. Interestingly, with  $[\text{HMMIM}]\text{Cl}$  (HMMIM = 1-hexyl-2,3-dimethylimidazolium) where the blocked C-2 position prevents carbene complex formation,  $[\text{PdCl}_4]^{2-}$  is formed rather than the metal. This is clearly the result of the relative coordinating strengths of the  $\text{Cl}^-$  anion in comparison to  $[\text{BF}_4]^-$  and  $[\text{PF}_6]^-$ . In this study palladium acetate itself was never found to be stable in solution in the ionic liquid. When the experiment was repeated in the presence of  $\text{PPh}_3$ ,  $[\text{HMMIM}]\text{Cl}$  yielded  $[\text{PdCl}_2(\text{PPh}_3)_2]$  while  $[\text{HMIM}]\text{Cl}$  still gave



**Scheme 5.3-22** Pd-catalyzed, regioselective arylation of butyl vinyl ether in an [BMIM][BF<sub>4</sub>] ionic liquid.

[PdCl<sub>2</sub>(HMimy)<sub>2</sub>]. However, when the [BF<sub>4</sub>]<sup>−</sup> and [PF<sub>6</sub>]<sup>−</sup> ionic liquids were studied under these conditions, nanoparticulate palladium (0.8–1.6 nm diameter) was seen.

The situation might be different if bidentate phosphine ligands were used. This is at least indicated by another study by Xiao's group. They investigated the regioselective arylation of butyl vinyl ether using again Pd(OAc)<sub>2</sub> as catalyst precursor in [BMIM][BF<sub>4</sub>] but the ligand in use was 1,3-bis(diphenylphosphino)propane (dppp) (Scheme 5.3-22) [205].

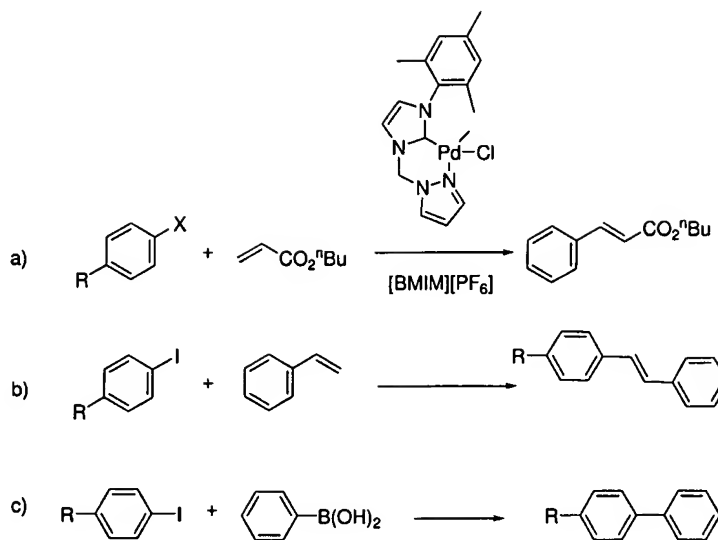
They compared the results in ionic liquids with those obtained in four conventional organic solvents. Interestingly, no formation of palladium black was observed in the ionic liquid while this was always the case with the organic solvents. Furthermore, the reaction in the ionic liquid proceeded with very high selectivity to the α-arylated compound whereas variable mixtures of the α- and β-isomers were obtained in the organic solvents DMF, DMSO, toluene and acetonitrile.

In recent times, many Heck coupling reactions have been carried out using Pd nanoparticles that were previously prepared for this purpose in ionic liquids. These examples will be presented in Section 5.3.2.7 which is entirely devoted to nanoparticulate catalysis in ionic liquids.

#### Heck reactions with Pd-complexes carrying carbenes or ionic ligands

Besides their *in situ* formation, carbene ligands have also been synthesized deliberately as alternatives to phosphine ligands for application in the Pd-catalyzed Heck reaction. For example, Shreeve et al. synthesized a NHC bearing catalyst (Scheme 5.3-23) for Heck and Suzuki coupling reactions, which was immobilized in [BMIM][PF<sub>6</sub>] [206]. This air and moisture stable catalyst was tested in several reactions with good yields in up to six recycling experiments. For the Heck cross-coupling reaction of aryl halides with n-butyl acrylate (Scheme 5.3-23(a)) the yields were in the range 68–94%, dependent on R. The catalyst dissolved in ionic liquid could be recycled up to six times. For Heck cross-coupling reactions of aryl halides with styrene (Scheme 5.3-23(b)) and for Suzuki coupling reactions (Scheme 5.3-23(c)) yields around 90% were realized and up to five recycling runs of the ionic catalyst solution could be demonstrated.

A particularly successful concept for catalyst immobilization in ionic liquids is the use of ionic ligands. Some examples of Pd-complexes carrying ionic ligands that have been applied in Heck reactions are listed in Table 5.3-9. Entries 1 and



**Scheme 5.3-23** Pd-carbene catalyst as synthesized and applied for Heck and Suzuki coupling reactions in [BMIM][PF<sub>6</sub>] by Shreeve and coworkers.

3 gave high yields and good recyclability results with up to 11 cycles. The oxime carbapalladacycle (entry 2) gave low yields. This observation was ascribed to the possibility of carbene formation at the imidazolium functional group under the basic conditions necessary for the reaction. This and a rather low ligand stability may explain the observed, significant palladium leaching. Significant leaching was also found when supporting this imidazolium-modified carbapalladacycle catalyst on Al/MCM-41 and using the resulting solid as a SILP Heck catalyst.

#### Ligand-less Heck reaction in ionic liquids

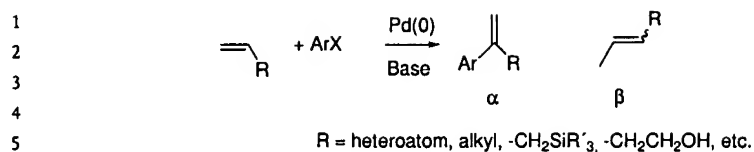
A special focus of modern research in Pd-catalyzed Heck-coupling reactions is to investigate the ligand-free reaction in ionic liquids using Pd(OAc)<sub>2</sub>, PdCl<sub>2</sub> or Pd/C as catalyst precursors [210]. In these examples the role of the ionic liquid is as either solvent, ligand or both. Of special interest for these studies is the regioselectivity of the Heck products when electron-rich olefins, such as acyclic enol ethers, silanes, and enol amides are applied as substrates. Possible products are the branched olefin ( $\alpha$ , Scheme 5.3-24) and the linear olefin ( $\beta$ , Scheme 5.3-24).

The formation of the different products can be explained by two reaction pathways, with a non-polar transition state leading to the linear olefin (Scheme 5.3-25, Path A) and a polar transition state to branched olefins (Scheme 5.3-25, Path B). Hallberg and coworkers demonstrated that the regiocontrol in the arylation of electron-rich olefins such as enol ethers is governed by a range of parameters, including, among others, the electronic properties of the aromatic ring and the choice

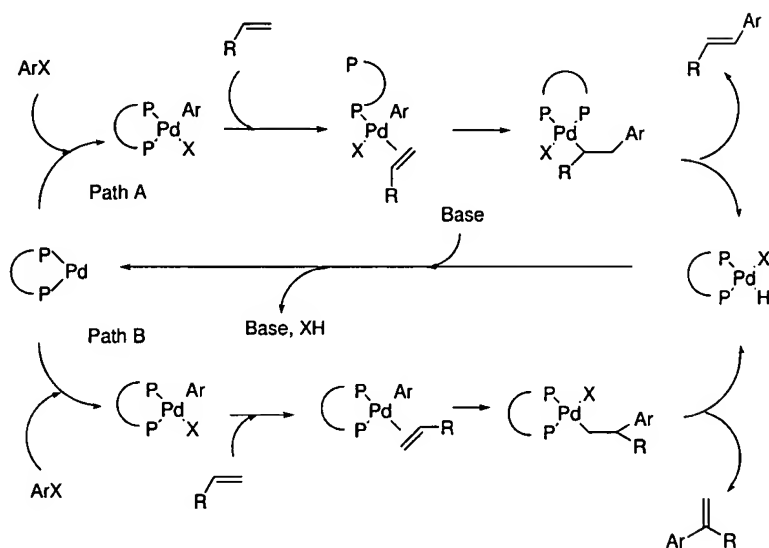
Table 5.3-9 Examples of ionic liquids as ligand for Heck<sup>[a]</sup>, Suzuki<sup>[b]</sup> and Sonogashira<sup>[d]</sup> reactions.

Entry	Catalyst	Dissolved in	No. of recycling cycles	Ref.
1 <sup>[a]</sup>			11	[207]
2 <sup>[a,b]</sup>			5	[208]
3 <sup>[a,b,c]</sup>			9	[209]

## 424 | 5 Organic Synthesis



Scheme 5.3-24 Regioselectivity in Heck reactions with electron-rich olefins.



Scheme 5.3-25 Regioselectivity of the Heck reaction.

of ligands and halide additives [211]. From earlier work it is known that addition of stoichiometric quantities of thallium or silver salt, replacement of arylating halides by triflate and use of bidentate ligands promote the predominant formation of the branched product [212].

Xiao et al. [213] recently reported that the intermolecular Heck arylation with several electron-rich olefins can be effected with both aryl bromides and iodides in a highly regioselective manner by the use of ionic liquids. Regioselectivity towards the branched  $\alpha$ -olefin was up to 99/1 and there was no need for additional halide scavenger. In this case the ionic liquid seems to serve not only as a quite polar solvent but also as halide scavenger.

**Application-oriented Heck studies in ionic liquids**

Seddon's group described the option of carrying out Heck reactions in ionic liquids that do not completely mix with water. These authors studied different Heck reactions in the triphasic system [BMIM][PF<sub>6</sub>]/water/hexane [214]. While the [BMIM]<sub>2</sub>[PdCl<sub>4</sub>] catalyst remained in the ionic liquid, the products dissolved in

the organic layer. The salt formed as a by-product of the reaction ( $[\text{H-base}]\text{X}$ ) was extracted into the aqueous phase.

An example of a continuous Heck reaction using a microflow system was reported by Liu and coworkers [215]. Their reaction was catalyzed by a  $[\text{Pd}(\text{PPh}_3)\text{Cl}_2(\text{BMim})]$  carbene complex, which was immobilized in the ionic liquid  $[\text{BMIM}][(\text{CF}_3\text{SO}_2)_2\text{N}]$ . The coupling product, butyl cinnamate, was produced in an overall yield of 80% ( $115.3 \text{ g}, 10 \text{ g h}^{-1}$ ), the ionic liquid containing Pd catalyst was continuously recycled. Unfortunately, the authors do not comment on the Pd leaching into the organic phase during their continuous operation.

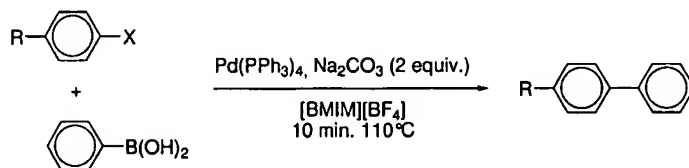
A highly thermally stable (up to  $280^\circ\text{C}$ ), Heck active catalyst system was obtained by Enders and coworkers through covalent anchoring of a N-heterocyclic carbene palladium/ionic liquid matrix on a silica surface [216]. Pd-NHC complexes were generated *in situ* in an imidazolium-type ionic liquid matrix (pre-functionalized with a trimethoxysilylpropyl group) grafted on a silica surface. With this system aryl iodides and bromides were rapidly (2–24 h) converted to the corresponding Heck products with excellent yields (81–99%) depending on the sort of olefin substrate. The catalyst was reused four times without loss of activity, giving a total TON of 36 600. Investigation of the catalyst after reaction by TEM and EDX showed again the formation of Pd nanoparticles (10–40 nm), which were obviously immobilized on the silica surface in an excellent manner as no leaching of palladium in the organic phase was observed.

A non-covalent immobilization of Heck catalyst on silica (SILP concept) has been realized by Hagiwara *et al.* [217]. They used a silica surface, supported with  $\text{Pd}(\text{OAc})_2$  dissolved in  $[\text{BMIM}][\text{PF}_6]$ . This catalyst was applied to the Mizoroki–Heck reaction of aryl halides with acrylate without a ligand in n-dodecane as solvent. It was six times reused and the overall TON reached 68 400 (for more details see Section 5.6).

#### Other Pd-catalyzed C–C-coupling reactions

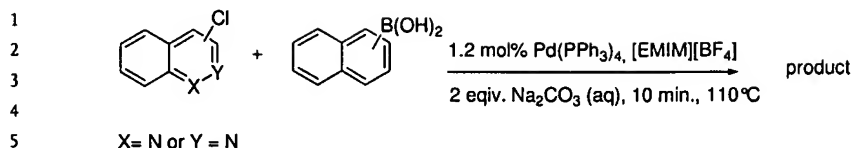
Closely related to Heck coupling, the Suzuki cross-coupling reaction (the coupling reaction of a halogenoarene with an arylboronic acid or ester) [218] has also been successfully performed in ionic liquids. Welton *et al.* used  $\text{Pd}(\text{PPh}_3)_4$  as catalyst in  $[\text{BMIM}][\text{BF}_4]$  to convert bromo- and iodoarenes with phenylboronic acid (Scheme 5.3-26) [219].

The best results were achieved by pre-heating the aryl halide in the ionic liquid with the Pd-complex to  $110^\circ\text{C}$ . The arylboronic acid and  $\text{Na}_2\text{CO}_3$  were later



Scheme 5.3-26 Pd-catalyzed Suzuki cross-coupling reaction in a  $[\text{BMIM}][\text{BF}_4]$  ionic liquid.

## 426 | 5 Organic Synthesis



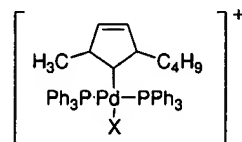
Scheme 5.3-27 Suzuki cross-couplings of heterocyclic chloroarenes with naphthaleneboronic acids in [EMIM][BF<sub>4</sub>].

10 added to start the reaction. Several advantages over the reaction performed under  
11 the conventional Suzuki conditions were described. The reaction showed signif-  
12 icantly enhanced activity in the ionic liquid (TOF = 455 h<sup>-1</sup> in [BMIM][BF<sub>4</sub>] in  
13 comparison to 5 h<sup>-1</sup> under conventional Suzuki conditions). The formation of the  
14 homo-coupling aryl by-product was suppressed. Moreover, the ionic catalyst layer  
15 could be reused after extraction of the products with ether and removal of the by-  
16 products NaHCO<sub>3</sub> and NaXB(OH)<sub>2</sub> with excess water. Over three further reaction  
17 cycles no deactivation was observed using this protocol.

18 Later, the catalyst complex [Pd(PPh<sub>3</sub>)<sub>4</sub>] dissolved in [EMIM][BF<sub>4</sub>] was successfully  
19 applied for the coupling of heterocyclic chloroarenes with naphthaleneboronic acids  
20 (Scheme 5.3-27) [220]. Products were obtained in higher yields (43–81%, enhanced  
21 reaction rate and improved selectivity) compared to conventional organic solvent.

22 In the light of the discussion on the potential role of Pd–carbene complexes in  
23 coupling reactions in ionic liquids it is of particular interest to note that an addition  
24 of halide ions to the reaction solution was reported to be necessary to form stable  
25 Suzuki coupling systems [219]. Investigations by Welton and coworkers in which  
26 the catalytically active solutions were analyzed in more detail revealed indeed the  
27 presence of a mixed phosphine–imidazolyliene palladium complex (Fig. 5.3-15)  
28 [221]. The cation 1-butyl-2-phenyl-3-methylimidazolium could be identified in the  
29 reaction mixture [222]. This ion is likely to form by reductive elimination from a pal-  
30 ladium species containing both a phenyl ring and a BMimy ligand thus confirming  
31 the involvement of the related Pd–carbene complex in the catalytic process.

32 Interestingly, Suzuki coupling in ionic liquids has also been reported in  
33 the absence of any phosphine ligand. When [(CH<sub>3</sub>CN)<sub>2</sub>PdCl<sub>2</sub>] was dissolved in  
34



42 X = Cl or Br

43 Fig. 5.3-15 Phosphine-imidazolyliene palladium ion  
44 [(BMimy)(PPh<sub>3</sub>)<sub>2</sub>PdX]<sup>+</sup> as identified from the reaction mixture of a  
45 Suzuki reaction in [BMIM][BF<sub>4</sub>].



preferentially [BMPy][ $(\text{CF}_3\text{SO}_2)_2\text{N}$ ] or [BMMIM][ $\text{BF}_4$ ] together with four equivalents of an imidazol derivative (best results gave 1-phenylimidazole and 1-methylbenzimidazole) and this mixture was heated, the Suzuki reaction proceeded with a TOF of up to  $221 \text{ h}^{-1}$ . To learn more about this sort of catalysis Welton and coworkers added aqueous  $\text{Na}_2\text{CO}_3$  solution as a base to the catalytic mixture and analyzed the resulting mixture by ESI-MS. Among several unidentified palladium-complexes they could identify the carbene complex  $[(\text{MIM})_2\text{Pd}(\text{BMimy})\text{Cl}]^+$  which is likely to be the catalytic active species [223]. Remarkably, no carbene-complex was built by heating  $[(\text{CH}_3\text{CN})_2\text{PdCl}_2]$  in the ionic liquid itself without additional aqueous  $\text{Na}_2\text{CO}_3$  solution.

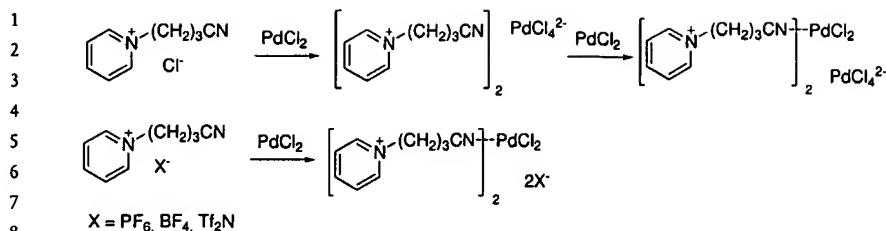
A certain pre-treatment was also found to be necessary for the Ni-catalyzed Suzuki coupling. Iwasawa's group found that the addition of anhydrous  $\text{K}_3\text{PO}_4$  improved the reactivity of  $[\text{BMIM}][\text{NiCl}_4]$  significantly and they suggested that by addition of this weak base the catalytically active nickel carbene complex can form. With no addition of phosphine ligand the reaction of 4-chlorotoluene and phenylboronic acid gave a yield of 23%, which could be improved up to 96% after addition of two equivalents of  $\text{PPh}_3$  [82]. This catalytic system was also immobilized on silica. The immobilization made the pretreatment rather complicated (treatment with  $\text{NaOtBu}$  for 30 min at room temperature followed by addition of  $\text{PPh}_3$ ) and the pre-treatment had to be repeated for every single reuse. Nevertheless, yields up to 93% for the first two runs could be realized with this immobilized system which decreased to 69% and 64% yield in the following runs.

Further examples of phosphine-free Pd-catalyzed Suzuki coupling were reported by Shreeve et al. [224]. They applied the monoquaternary 2,2'-biimidazolium-based ionic liquid shown above in Table 5.3-9 (entry 1) as ionic liquid and ligand and reported good results for the transformation of phenylboronic acid with chlorobenzene derivatives. The system remained active for 14 consecutive runs with yields of 80–90%, depending on the electron-donating or -withdrawing properties of the substituents at the chlorobenzene substrate.

The Suzuki reaction has also been carried out in ionic liquids using ultrasound irradiation as an energy source [225]. For the reaction in  $[\text{BMIM}][\text{BF}_4]$  significant *homo*-coupling of phenylboronic acid was reported when the reaction was performed in air. In this case, decomposition of the Pd-complex prevented repetitive catalytic runs. However, when the imidazolydene complex  $[\text{PdX}_2(\text{BBimy})_2]$  was independently prepared and used as the source of palladium, comparable conversions to  $\text{Pd}(\text{OAc})_2$  were observed. However, in this case no decomposition to Pd metal or *homo*-coupling was observed in the experiment under otherwise identical conditions. The complex  $[\text{PdX}_2(\text{BBimy})_2]$  could be quantitatively recovered from the catalytic mixture and used in three repetitive catalytic runs for the reaction of 4-bromoanisole with phenylboronic acid with only a slight decrease in activity. In contrast to ultrasound-irradiated Heck reactions with the same complex under similar conditions [226] no evidence of Pd nanoparticle formation could be found in the Suzuki reactions.

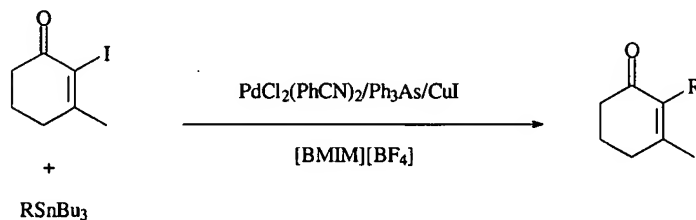
To achieve a better Pd-immobilization in the ionic liquid, Dyson et al. synthesized and applied *N*-butyronitrile pyridinium ionic liquids (Scheme 5.3-28) [227]. Indeed,

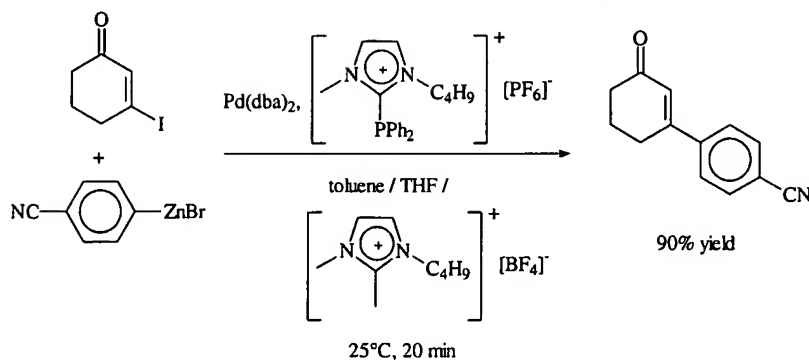
## 428 | 5 Organic Synthesis

Scheme 5.3-28 PdCl<sub>2</sub> immobilization in *N*-butyronitrile functionalized pyridinium ionic liquids.

the leaching of palladium into the organic layer was significantly less than in the non-functionalized pyridinium system. The method led also to the isolation of the nitrile-stabilized palladium complex that was found to be air stable and did not decompose on washing with water or alcohols at room temperature. However, decomposition was observed when contacting the complex with water or alcohols over prolonged periods of time. The catalyst/ionic liquid system was evaluated in the Suzuki coupling reaction of iodobenzene and phenylboronic acid and in the Stille coupling reaction of iodobenzene and phenyltributylstannane. Catalyst immobilization in the nitrile-functionalized ionic liquid enabled recycling for 9 runs without significant loss of activity (all yield >80%). In contrast, immobilization in the non-functionalized ionic liquid [BPy][(CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>N] led to complete deactivation after 6 runs. In contrast to the Suzuki coupling reaction, significant nanoparticle formation was observed for the Stille coupling. Transmission electron microscopy (TEM) analysis of the particles formed *in situ* in the Stille reaction reveals that the nitrile-functionalized ionic liquid exerts a superior nanoparticle-stabilizing effect compared to the non-functionalized ionic liquid.

A number of other Stille coupling reactions have also been reported by Handy et al. [228]. Using [PdCl<sub>2</sub>(PhCN)<sub>2</sub>]/Ph<sub>3</sub>As/CuI in [BMIM][BF<sub>4</sub>] good yields and good catalyst recyclability (up to five times) were reported for the reaction of α-iodoenones with vinyl and aryl stannanes (Scheme 5.3-29). However, the reported reaction rates were significantly lower than those obtained in *N*-methylpyrrolidinone (NMP). Additional examples of Stille coupling reactions in different ionic liquids have been more recently reported by Chiappe's group [229].

Scheme 5.3-29 Pd-catalyzed Stille coupling of α-iodoenones with vinyl and aryl stannanes in [BMIM][BF<sub>4</sub>].



**Scheme 5.3-30** Pd-catalyzed cross-coupling of organozinc compounds (Negishi cross-coupling) in [BMMIM][BF<sub>4</sub>].

Also Pd-catalyzed Negishi cross-coupling reactions have been described in ionic liquids. Knochel and coworkers investigated the reaction between organometallic zinc compounds and aryl iodide in [BMMIM][BF<sub>4</sub>] using an ionic phosphine ligand. Scheme 5.3-30 illustrates the reaction for the formation of a 3-substituted cyclohexenone from 3-iodo-2-cyclohexen-1-one [170]. The reaction was carried out in an ionic liquid/toluene biphasic system, which allowed easy product recovery from the catalyst by decantation. However, attempts to recycle the ionic catalyst phase resulted in significant catalyst deactivation, after only the third recycle.

Finally, it should be mentioned that Pd-catalyzed allylations [230, 231], allylic alkylation [231] and substitution [232] reactions as well as Trost-Tsuji-coupling [233] have also been carried out in different ionic liquids with some success.

In summary it can be stated that low melting salts and ionic liquids are very interesting reaction media for Pd-catalyzed coupling reactions. However, the role of the ionic liquid is variable and may be very complex. Ionic liquids have been found to act as solvents, ligands, ligand precursors and dispersants. In many cases more than one of these functions was taken by the ionic reaction medium. 1,3-dialkylimidazolium ionic liquids, especially, are often not inert under the reaction conditions. Moreover, the formation of Pd nanoparticles has always to be taken into account as a possible explanation for the observed results. These particles seem to be stabilized in the ionic liquids (see Sections 5.3.2.7 and 6.3 for more details) and the resulting mixtures have shown excellent catalytic performance in at least some cases.

#### 5.3.2.5 Dimerization and Oligomerization Reactions

Biphasic catalysis is not a new concept for catalytic oligomerization chemistry. On the contrary, the oligomerization of ethylene was the first commercial example of a biphasic, transition metal catalyzed reaction. The process is known under the name "Shell higher olefins process (SHOP)" and the first patents originate from as early as the late sixties [234]. While the SHOP uses 1,4-butanediol as the catalyst phase,

## 430 | 5 Organic Synthesis

1 it turned out in the following years of research that many highly attractive catalyst  
 2 systems for dimerization and oligomerization are not compatible with polar organic  
 3 solvents or water. This is because high electrophilicity of the metal center is a key  
 4 prerequisite for catalytic activity in oligomerization. The higher the electrophilicity  
 5 of the metal center the higher usually is its catalytic activity but the lower, at the  
 6 same time, is its compatibility with polar organic solvents or water. Consequently,  
 7 many cationic transition metal complexes are excellent oligomerization catalysts  
 8 [43] but none of these systems could be realized in a biphasic reaction mode using  
 9 water or polar organic solvents as the catalyst phase.

#### 12 Chloroaluminate-based dimerization and oligomerization systems

13 One example of a technically important oligomerization reaction that could not be  
 14 carried out in a liquid–liquid biphasic mode prior to the invention of chloroalumi-  
 15 nate ionic liquids is the Ni-catalyzed dimerization of propene and/or butenes. This  
 16 reaction was intensively studied in the sixties [235] and commercialized later as the  
 17 “Dimersol-process” by the Institut Français du Pétrole (IFP). In this reaction the  
 18 active catalytic species forms *in situ* by reaction of a Ni(II)-source and an aluminum  
 19 alkyl co-catalyst. In the conventional process the reaction takes place in a monopha-  
 20asic reaction mode in an organic solvent or – technically preferred – in the alkene  
 21 feedstock. After reaction the catalyst is destroyed by addition of an aqueous solution  
 22 of a base and the precipitated Ni salt is filtered off and has to be disposed of. 25  
 23 Dimersol units are currently in operation producing octane booster for gasoline with  
 24 a total processing capacity of 3.4 Mtons per year. Taking into account the significant  
 25 consumption of nickel and aluminum alkyls related to the monophasic Dimersol  
 26 process it is not surprising that IFP research teams were looking for new solvent  
 27 concepts to allow a biphasic version of the Dimersol chemistry. Chloroaluminate  
 28 ionic liquids proved to be highly attractive in this respect.

29 As early as 1990, Chauvin and his coworkers from IFP published their first results  
 30 on the biphasic, Ni-catalyzed dimerization of propene in ionic liquids of the type  
 31 [BMIM]Cl/AlCl<sub>3</sub>/AlEtCl<sub>2</sub> [4]. In the following years the nickel-catalyzed oligomer-  
 32 ization of short-chain alkenes in chloroaluminate melts became one of the best  
 33 investigated applications of transition metal catalysts in ionic liquids to the present.

34 Due to its importance, some basic principles of the Ni-catalyzed dimerization of  
 35 propene in chloroaluminate ionic liquids should be presented here. Table 5.3-10  
 36 displays some reported examples, which have been selected to explain the most im-  
 37 portant aspects of oligomerization chemistry in chloroaluminate ionic liquids [236].

38 The Ni-catalyzed oligomerization of olefins in ionic liquids requires a careful  
 39 choice of the ionic liquid's acidity. In basic melts (Table 5.3-10, entry (a)) no dimer-  
 40 ization activity is observed. Here, the basic chloride ions prevent the formation of  
 41 free coordination sites on the nickel catalyst. In acidic chloroaluminate melts, an  
 42 oligomerization reaction takes place even in the absence of a nickel catalyst (entry  
 43 (b)). However, no dimers, but a mix of different oligomers, are formed by cationic  
 44 oligomerization. Superacidic protons and the reactivity of the acidic anions [Al<sub>2</sub>Cl<sub>7</sub>]<sup>–</sup>  
 45 and [Al<sub>3</sub>Cl<sub>10</sub>]<sup>–</sup> may account for this reactivity.

Table 5.3-10 Selected results of the Ni-catalyzed propene dimerization in chloroaluminate ionic liquids.<sup>a</sup>

	Ionic liquid	Composition of the ionic liquid (molar ratio)	Ni-complex	Activity kg/g(Ni) h <sup>-1</sup>	Product DMB/M2P/nH <sup>a</sup>
(a)	[BMIM]Cl/AlCl <sub>3</sub>	1/0.8	NiBr <sub>2</sub> L <sub>2</sub> <sup>b</sup>	0	
(b)	[BMIM]Cl/AlCl <sub>3</sub>	1/1.5		c	
(c)	[BMIM]Cl/AlEtCl <sub>2</sub>	1/1.2	NiCl <sub>2</sub>	2.5	5/74/21
(d)	[BMIM]Cl/AlEtCl <sub>2</sub>	1/1.2	NiCl <sub>2</sub> (iPr <sub>3</sub> P) <sub>2</sub>	2.5	74/24/2
(e)	[BMIM]Cl/AlCl <sub>3</sub> /AlEtCl <sub>2</sub>	1/1.2/0.1	NiCl <sub>2</sub> (Pr <sub>3</sub> P) <sub>2</sub>	12.5	83/15/2

T = -15°C;

<sup>a</sup>DMB = dimethylbutenes, M2P = methylpentenes, nH = n-hexenes,<sup>b</sup>L = 2-methylallyl;<sup>c</sup>highly viscous oligomers from cationic oligomerization were obtained.

The addition of aluminum alkyl compounds is known to suppress this undesired cationic oligomerization activity. In the presence of  $\text{NiCl}_2$  as catalyst precursor, the ionic catalyst solution is formed and shows high activity for the dimerization (entry (c)). Without added phosphine ligands, a product distribution is obtained with no particular selectivity. With added phosphine ligand, the distribution of regioisomers in the C6-fraction is influenced by the steric and electronic properties of the ligand used in the same way as known from the catalytic system in organic solvents [235] (entry (d)). At longer reaction times, a decrease in the selectivity to highly branched products is observed. It has been postulated that a competing reaction of the basic phosphine ligand with the hard Lewis acid  $\text{AlCl}_3$  takes place. This assumption is supported by the observation that the addition of a soft competing base such as tetramethylbenzene can prevent the loss in selectivity.

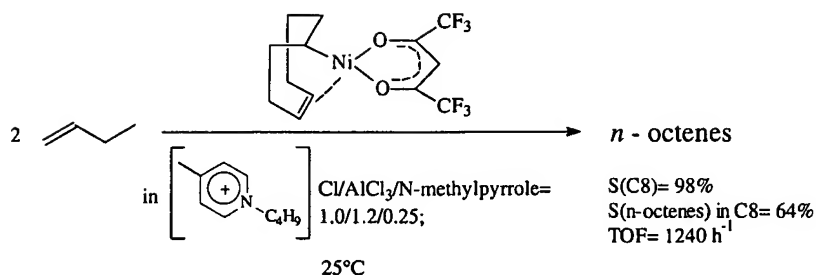
Unfortunately, investigations with ionic liquids containing high amounts of  $\text{AlEtCl}_2$  reveal several limitations: The reductive effect of the aluminum alkyl affects the temperature stability of the nickel catalyst. At very high aluminum alkyl concentrations, a precipitation of black metallic nickel is observed, even at room temperature.

Based on these results the Institut Français du Pétrole (IFP) has developed a biphasic version of their established monophasic “Dimersol” process, which is offered for licensing under the name “Difasol” process [237]. The “Difasol” process uses slightly acidic chloroaluminate ionic liquids with small amounts of aluminum alkyls as the solvent for the catalytic nickel center. In comparison to the established “Dimersol” process, the new biphasic ionic liquid process drastically reduces the consumption of Ni catalyst and aluminum alkyls. Additional advantages arise from the good performance obtained with highly diluted feedstocks and the significantly improved dimer selectivity of the “Difasol” process (for more detailed information see Section 5.4).

Wasserscheid and coworkers studied the selective, Ni-catalyzed, biphasic dimerization of 1-butene to linear octenes. Therefore, a catalytic system that is well-known for its ability to form linear dimers from 1-butene in conventional organic solvents [238] – namely the square planar Ni-complex ( $\eta$ -4-cycloocten-1-yl)(1,1,1,5,5,5-hexafluoro-2,4-pentandionato-O,O')nickel,  $[(\text{H-COD})\text{Ni}(\text{hfacac})]$  – was used in chloroaluminate ionic liquids.

For this specific task, ionic liquids containing aluminum alkyls proved to be unsuitable, due to their strong isomerization activity [241]. Since, mechanistically, only the linkage of two 1-butene molecules can lead to the formation of linear octenes, isomerization activity of the solvent inhibits the formation of the desired product. Therefore, slightly acidic chloroaluminate melts that enable selective nickel catalysis without the addition of aluminum alkyls have been developed [239]. It was found that an acidic chloroaluminate ionic liquid buffered with small amounts of weak organic bases provides a solvent which allows a selective, biphasic reaction using nickel  $[(\text{H-COD})\text{Ni}(\text{hfacac})]$ .

The function of the base is to trap any free acidic species in the melt which might initiate cationic side reactions. A suitable base has to fulfill a number of requirements. Its basicity has to be in the appropriate range to provide enough



**Scheme 5.3-31** Ni-catalyzed, biphasic, linear dimerization in a slightly acidic, buffered chloroaluminate ionic liquid.

reactivity to eliminate all free acidic species in the melt. At the same time, it has to be non-coordinating with respect to the catalytically active Ni center. Another important feature is a very high solubility in the ionic liquid. During the reaction, the base has to remain in the ionic catalyst layer, even under intense extraction of the ionic liquid by the organic layer. Finally, the base has to be inert to the 1-butene feedstock and the oligomerization products.

The use of pyrrole and *N*-methylpyrrole was found to be preferred. By the addition of *N*-methylpyrrole, all cationic side reactions could be effectively suppressed and only dimerization products produced by Ni catalysis were obtained. In this case the dimer selectivity was as high as 98%. Scheme 5.3-31 shows the catalytic system that allowed the first successful application of  $[(\text{H-COD})\text{Ni}(\text{hfacac})]$  in the biphasic linear dimerization of 1-butene.

The comparison of the dimerization of 1-butene with  $[(\text{H-COD})\text{Ni}(\text{hfacac})]$  in chloroaluminate ionic liquids with the identical reaction in toluene is quite instructive. First, the reaction in the ionic liquid solvent is biphasic with no detectable catalyst leaching, enabling easy catalyst separation and recycling. While  $[(\text{H-COD})\text{Ni}(\text{hfacac})]$  requires an activation temperature of 50 °C in toluene, the reaction proceeds in the ionic liquid even at -10 °C. This indicates that the catalyst activation, which is believed to be the formation of the active Ni-hydride complex, proceeds much more efficiently in the chloroaluminate solvent (for more details on mechanistic studies see Section 5.3.1.3). Furthermore, the product selectivities obtained in both solvents reveal significantly higher dimer selectivities in the biphasic case. This can be understood by considering the fact that the C8-product is much less soluble in the ionic liquid than the butene feedstock (by about a factor 4). During the reaction, a fast extraction of the C8-product into the organic layer takes place, thus preventing consecutive C12-formation. The linear selectivity is high in both solvents, however, somewhat lower in the ionic liquid solvent.

To create reliable data on the lifetime and overall activity of the ionic catalyst system, a loop reactor was constructed and the reaction was carried out in continuous mode [240]. The most important results of these studies are presented in

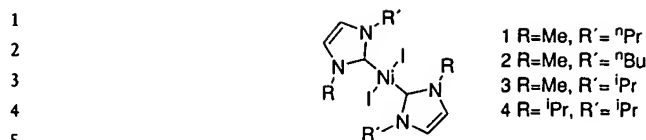


Fig. 5.3-16 Ni-carbene complexes as used in the dimerization of propene and 1-butene in chloroaluminate ionic liquids.

Section 5.4, together with much more detailed information about the processing of biphasic reactions with an ionic liquid catalyst phase.

$[\text{Ni}(\text{MeCN})_6][\text{BF}_4]_2$  dissolved in the slightly acidic chloroaluminate system  $[\text{BMIM}]\text{Cl}/\text{AlCl}_3/\text{AlEtCl}_2$  (ratio = 1:1.2:0.25) has also been used for the dimerization of butenes [241]. The reaction showed high activity even at 10 °C and under atmospheric pressure with a turnover frequency of  $6840 \text{ h}^{-1}$  and a productivity of 6 kg oligomer per gram Ni per hour. The distribution of the butene dimers obtained (typically  $39 \pm 1\%$  dimethylhexenes,  $56 \pm 2\%$  monomethylheptenes and  $6 \pm 1\%$  n-octenes) was reported to be independent of the addition of phosphine ligands. Moreover, the product mix was independent of feedstock, with both 1-butene and 2-butene yielding the same dimer distribution, with only 6% of the linear product. This clearly indicates that the catalytic system used here is not only an active oligomerization catalyst but is also highly active for isomerization.

In our group nickel carbene complexes (Fig. 5.3-16) dissolved in slightly acidic, buffered chloroaluminate ionic liquids have been applied for the dimerization of propene and 1-butene [242].

Interestingly these complexes showed high activity without addition of alkyl aluminum compounds in the ionic liquid while they are almost inactive in toluene. These results are interpretable in terms of catalyst stabilization by the imidazolium-based ionic liquid. Reductive elimination of imidazolium is also possible as in toluene as in the ionic liquid but in the ionic liquid, a rapid reoxidation via addition of the solvent imidazolium cation seems possible and may prevent the formation of  $\text{Ni}^0$  deposits associated with catalyst deactivation. The carbene complex with  $\text{R} = \text{n-Bu}$  showed the highest activity with a dimer yield of 70.2% ( $\text{TOF} = 7020 \text{ h}^{-1}$ ). The preferred product of the nickel-carbene catalyzed reaction is methylpentene. Additional phosphine ligand had no significant influence on the distribution of the products in this case.

Catalytic systems based on chloroaluminate ionic liquids have also been used for the selective dimerization of ethene to butenes [243]. Dupont et al. dissolved  $[\text{Ni}(\text{MeCN})_6][\text{BF}_4]_2$  in the slightly acidic chloroaluminate system  $[\text{BMIM}]\text{Cl}/\text{AlCl}_3/\text{AlEtCl}_2$  (ratio = 1:1.2:0.25) and obtained 100% butenes at  $-10^\circ\text{C}$  and 18 bar ethylene pressure ( $\text{TOF} = 1731 \text{ h}^{-1}$ ). Unfortunately, the more valuable 1-butene was not produced selectively but a mixture of all linear butene isomers was obtained. The active nickel catalyst is formed *in situ* in the ionic liquid by reaction of the precursor with the alkylaluminum(III) species in the ionic liquid.



1 Later, de Souza et al. compared the reactivity of  $[\text{Ni}(\text{MeCN})_6][\text{BF}_4]_2$  (activated with  
2  $\text{AlEt}_2\text{Cl}$  or  $\text{AlEt}_3$  as cocatalysts) in the homogeneous phase, immobilized in ionic liq-  
3 uids, and heterogenized in zeolite [244]. They found that in the homogeneous phase  
4 the Ni catalyst showed high activity ( $\text{TOF} = 2451 \text{ h}^{-1}$ ) and 97% selectivity to C4 prod-  
5 ucts (with 30% 1-butene in C4) under mild conditions was obtained. Under biphasic  
6 conditions, when the catalyst was immobilized in  $[\text{BMIM}]\text{Cl}/\text{AlCl}_3/\text{AlEtCl}_2$ , ethy-  
7 lene dimerization occurred with 83% selectivity to 1-butene. Finally, immobilization  
8 of the catalyst in zeolite NaX gave 78% selectivity to 1-butene.

9 Further comparison of the homogenous and biphasic conditions for the oligomer-  
10 ization of ethene was carried out in chloroaluminate systems by de Souza and  
11 coworkers using nickel-1,2-diiminophosphorane complexes. They found, that the  
12 catalyst had a very much higher activity for ethylene oligomerization when immobi-  
13 lized in a  $[\text{BMIM}]\text{Cl}/\text{AlCl}_3/\text{AlEt}_2\text{Cl}$ -system than in a homogeneous (chlorobenzene)  
14 phase [245]. The catalyst could be easily recycled in the chloroaluminate system with  
15 increasing catalyst activity from the first to the third cycle. Possible reasons for this  
16 surprising behavior are discussed, such as displacement of the diiminophospho-  
17 rane ligand leading to new highly active catalytic species. The selectivity to 1-olefins  
18 was also improved in the ionic liquid but was still very low due to significant iso-  
19 merization activity of the catalytic system in use.

20 Biphasic ethylene oligomerization reactions have also been described in chloroa-  
21 luminate ionic liquids using catalytic metals other than nickel. Olivier-Bourbigou  
22 et al. dissolved the tungsten complex  $[\text{Cl}_2\text{W}=\text{NPh}(\text{PMe}_3)_3]$  in a slightly acidic  
23  $[\text{BMIM}]\text{Cl}/\text{AlCl}_3$  system and used this ionic catalyst solution in ethylene oligomer-  
24 ization without adding a co-catalyst [246]. At  $60^\circ\text{C}$  and 40 bar a product distribution  
25 containing 81% butenes, 18% hexenes and 1% higher oligomers was obtained with  
26 good activity ( $\text{TOF} = 1280 \text{ h}^{-1}$ ). However, the selectivity for the more valuable  
27 1-olefins was found to be relatively low (65%).

28 The selective, chromium catalyzed trimerization of ethylene to 1-hexene was  
29 disclosed in a patent by SASOL [247]. In this work a biphasic reaction system was  
30 explored using alkylchloroaluminate ionic liquids as the catalyng phase.

### 34 *Dimerization and oligomerization of olefins in non-chloroaluminate systems*

35 Biphasic oligomerization with ionic liquids is not restricted to chloroaluminate  
36 systems. Especially in those cases where the, at least, latent acidity or basicity of the  
37 chloroaluminate causes problems, neutral ionic liquids with weakly coordinating  
38 anions can be used with great success.

39 As already mentioned above, the Ni-catalyzed oligomerization of ethylene in  
40 chloroaluminate ionic liquids was found to be characterized by high oligomeriza-  
41 tion and high isomerization activity. The latter leads to a rapid consecutive trans-  
42 formation of the 1-olefins formed into mixtures of far less valuable internal olefins.  
43 Higher 1-olefins (HAOs) are an important group of industrial chemicals that find  
44 a variety of end uses. Depending on their chain length, they are components of  
45 plastics ( $\text{C}_4\text{--C}_6$  HAOs in copolymerization), plasticizers ( $\text{C}_6\text{--C}_{10}$  HAOs through

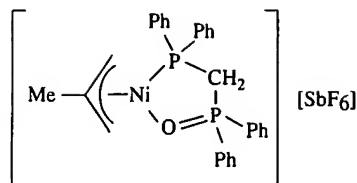


Fig. 5.3-17 The cationic Ni-complexes  $[(mAllyl)Ni(dppmo)][SbF_6]$  as used for the biphasic oligomerization of ethylene to 1-olefins in e.g. [BMIM][PF<sub>6</sub>].

hydroformylation), lubricants (C<sub>10</sub>–C<sub>12</sub> HAOs through oligomerization) and surfactants (C<sub>12</sub>–C<sub>16</sub> HAOs through arylation/sulfonation).

Besides the neutral nickel/phosphine complexes used in the SHOP, cationic Ni-complexes such as  $[(mAllyl)Ni(dppmo)][SbF_6]$  (see Fig. 5.3-17) have attracted some attention as highly selective and highly active catalysts for ethylene oligomerization to HAOs [248].

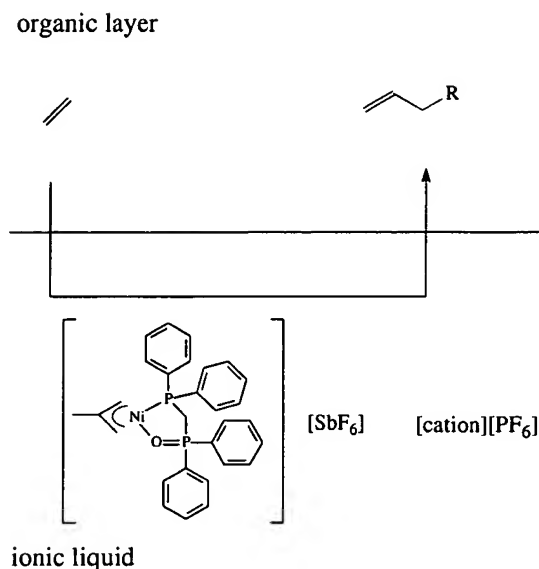
However, all attempts to carry out a biphasic ethylene oligomerization with this cationic catalyst using traditional organic solvents, such as 1,4-butanediol (which is used in the SHOP) resulted in almost complete catalyst deactivation by the solvent. This reflects the much higher electrophilicity of the cationic complex  $[(mAllyl)Ni(dppmo)][SbF_6]$  in comparison to the neutral Ni-complexes used in the SHOP.

Wasserscheid et al. demonstrated that the use of hexafluorophosphate ionic liquids allows, for the first time, a selective, biphasic oligomerization of ethylene to 1-olefins with the cationic Ni-complex  $[mAllylNi(dppmo)][SbF_6]$  (Scheme 5.3-32) [44, 249].

Obviously, the ionic liquid's ability to dissolve the ionic catalyst complex, combined with a low solvent nucleophilicity, opens up the possibility for biphasic processing. Furthermore, it was found that the biphasic reaction mode led, in this specific reaction, to improved catalytic activity, selectivity and to enhanced catalyst lifetime.

The higher activity of the catalyst  $[mAllylNi(dppmo)][SbF_6]$  in [BMIM][PF<sub>6</sub>] (TOF = 25425 h<sup>-1</sup>) vs. the reaction under identical conditions in CH<sub>2</sub>Cl<sub>2</sub> (TOF = 7591 h<sup>-1</sup>) can be explained by the fast extraction of products and side products out of the catalyst layer into the organic phase. A high concentration of internal olefins (from oligomerization and consecutive isomerization) at the catalyst is known to reduce catalytic activity due to the formation of quite stable Ni–olefin complexes.

The selectivity of the ethylene oligomerization reaction is clearly influenced by the biphasic reaction mode. The oligomers were found to be much shorter in the biphasic system, due to restricted ethylene availability at the catalytic center dissolved in the ionic liquid. This behavior correlates to the ethylene solubility in the different solvents under the reaction conditions. The ethylene solubility in 10 ml CH<sub>2</sub>Cl<sub>2</sub> was determined to be 6.51 g at 25 °C/50 bar vs. only 1.1 g ethylene dissolved in [BMIM][PF<sub>6</sub>] under identical conditions. Since the rate of ethylene insertion



**Scheme 5.3-32** Biphasic ethylene oligomerization with cationic Ni-complexes in a [BMIM][PF<sub>6</sub>] ionic liquid.

is dependent on the ethylene concentration at the catalyst, but the rate of  $\beta$ -H-elimination is not, it becomes understandable that low ethylene availability at the catalytic active center favors the formation of shorter oligomers. In good agreement with this, a shift of the oligomer distribution was observed if the ionic liquid's cation was modified with longer alkyl chains. With increasing alkyl chain length of the ionic liquid's cation the oligomer distribution obtained became gradually broader following the higher ethylene solubility in these ionic liquids. However, all biphasic oligomerization experiments still show much narrower oligomer distributions than in the case of the monophasic reaction in CH<sub>2</sub>Cl<sub>2</sub> (under identical conditions).

As well as the oligomer distribution, the selectivity to 1-olefins is of great technical relevance. Despite the much higher catalytic activity this selectivity was even slightly higher in [BMIM][PF<sub>6</sub>] compared to CH<sub>2</sub>Cl<sub>2</sub>. The overall 1-hexene selectivity in C<sub>6</sub>-products was found to be 88.5% in [BMIM][PF<sub>6</sub>] vs. 85.0% in CH<sub>2</sub>Cl<sub>2</sub>. Interestingly, less of the internal hexenes (formed by consecutive isomerization of 1-olefins) are obtained in the case of biphasic oligomerization using the ionic liquid solvent. This is explained by the much lower solubility of the higher oligomerization products in the catalyst solvent [BMIM][PF<sub>6</sub>]. Since the 1-olefins formed are quickly extracted into the organic layer, consecutive isomerization of these products at the Ni center is suppressed in comparison to the monophasic reaction in CH<sub>2</sub>Cl<sub>2</sub>.

It is noteworthy, that the best results could only be obtained with very pure ionic liquids and by using an optimized reactor set-up. The content of halide ions and water in the ionic liquid was found to be a crucial parameter since both impurities

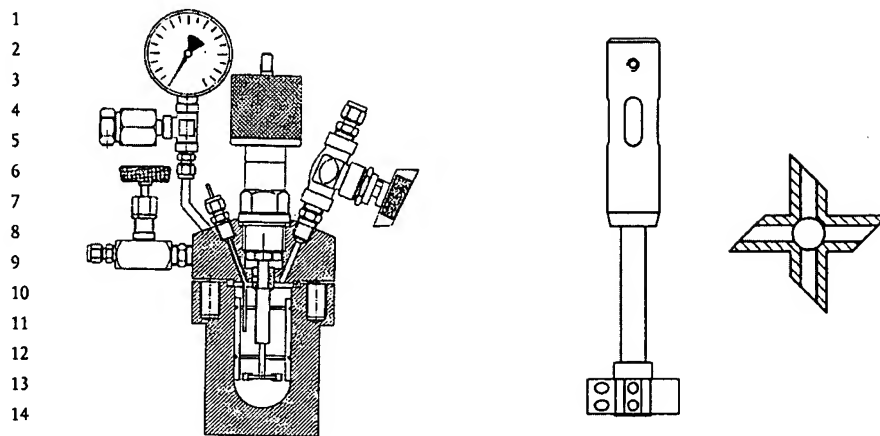


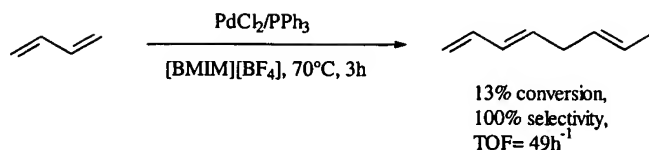
Fig. 5.3-18 150 ml autoclave with special stirrer design to maximize ethylene intake into an ionic liquid catalyst layer as used for the Ni-catalyzed liquid-liquid biphasic ethylene oligomerization in [BMIM][PF<sub>6</sub>].

poison the cationic catalyst. Furthermore, the catalytic results proved to be highly dependent on all modifications that influence the mass transfer rate of ethylene into the ionic catalyst layer. A 150 ml autoclave with baffles stirred from the top with a special gas entrainment stirrer (see Fig. 5.3-18) gave far better results than a standard autoclave stirred with a magnetic stirrer bar.

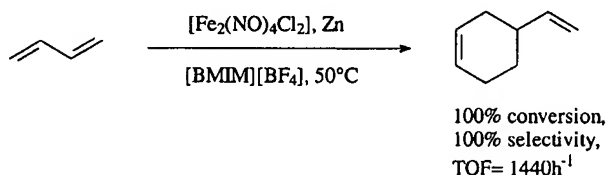
Finally, it could be demonstrated that the ionic catalyst solution can, in principle, be recycled. By repetitive use of the ionic catalyst solution an overall activity of 61 106 mol ethylene converted per mol catalyst could be realized after two recycle runs.

An example of a biphasic, Ni-catalyzed co-dimerization in ionic liquids with weakly coordinating anions was described by Leitner et al. [12]. The hydrovinylation of styrene was investigated in the biphasic system ionic liquid/compressed CO<sub>2</sub> using a chiral Ni catalyst. Since it was found that this reaction benefits particularly from this unusual biphasic solvent system more details about this specific application will be given in Section 5.7.

Dupont and coworkers studied the Pd-catalyzed dimerization [250] and the Fe-catalyzed cyclo-dimerization [251] of butadiene in non-chloroaluminate ionic liquids. The biphasic dimerization of butadiene is an attractive research goal since the products formed, 1,3,5-octatriene and 1,3,6-octatriene, are sensitive towards undesired polymerization, so that separation by distillation is usually not possible. These octatrienes are of some commercial relevance as intermediates for the synthesis of fragrances, plastizisers and adhesives. By using PdCl<sub>2</sub> with two equivalents of the ligand PPh<sub>3</sub> dissolved in [BMIM][PF<sub>6</sub>], [BMIM][BF<sub>4</sub>] or [BMIM][CF<sub>3</sub>SO<sub>3</sub>], it was possible to obtain the octatrienes with 100% selectivity (after 13% conversion) (Scheme 5.3-33) [250]. The turnover frequency (TOF) was in the range of 50 mol butadiene



Scheme 5.3-33 Biphasic, Pd-catalyzed dimerization of butadiene in  $[\text{BMIM}][\text{BF}_4]$ .



Scheme 5.3-34 Biphasic, Fe-catalyzed cyclotrimerization of butadiene in  $[\text{BMIM}][\text{BF}_4]$ .

converted per mol catalyst per hour, which represents a substantial increase in catalyst activity in comparison to the same reaction under identical conditions ( $70^\circ\text{C}$ , 3 h, butadiene/Pd = 1250) in THF (TOF =  $6\text{h}^{-1}$ ).

The cyclo-dimerization of 1,3-butadiene was carried out in  $[\text{BMIM}][\text{BF}_4]$  and  $[\text{BMIM}][\text{PF}_6]$  using an *in situ* iron catalyst system. The catalyst was prepared by reduction of  $[\text{Fe}_2(\text{NO})_4\text{Cl}_2]$  with metallic zinc in the ionic liquid. At  $50^\circ\text{C}$ , the reaction proceeded in  $[\text{BMIM}][\text{BF}_4]$  to give full conversion of 1,3-butadiene and 4-vinylcyclohexene was formed in 100% selectivity. The observed catalytic activity corresponded to a turnover frequency of at least  $1440\text{h}^{-1}$  (Scheme 5.3-34).

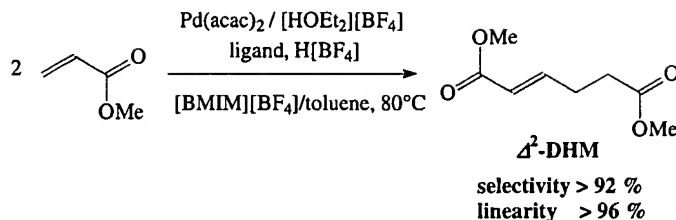
The authors correlate the observed catalytic activity to the solubility of the 1,3-butadiene feedstock in the ionic liquid, which was found to be two times higher in the tetrafluoroborate ionic liquid vs. the corresponding hexafluorophosphate system. It is noteworthy that the same reaction in a monophasic systems using toluene as the solvent was found to be significantly less active (TOF =  $240\text{h}^{-1}$ ).

#### Dimerization of functionalized olefins

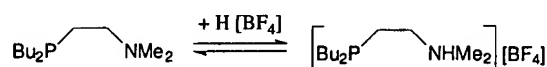
The dimerization of functionalized olefins is of general technical importance. For example, the dimerization of methylacrylate (MA) to  $\Delta^2$ -dihydrodimethylmuconate (DHM) leads to a highly interesting intermediate which can be transformed to both fine chemicals (such as cyclopentenones) and adipic acid. A continuous, liquid-liquid biphasic version of this Pd catalyzed reaction was realized by Tkatchenko et al. for the first time using  $[\text{BMIM}][\text{BF}_4]$ /toluene as reaction system (Scheme 5.3-35) [252].

While the monophasic reaction in organic solvents is known to suffer from product inhibition, the continuous reaction in the liquid-liquid biphasic system allowed one to overcome this limitation by *in situ* product extraction from the ionic catalyst phase. To avoid metal leaching out of the ionic liquid phase, the catalyst

## 440 | 5 Organic Synthesis



9 Scheme 5.3-35 Pd-catalyzed dimerization of methylacrylate in the  
10 biphasic system[BMIM][BF<sub>4</sub>]/toluene.



15 Scheme 5.3-36 *In situ* generated ammonium phosphine ligand as used  
16 for the continuous Pd-catalyzed dimerization of methylacrylate in the  
17 biphasic system[BMIM][BF<sub>4</sub>]/toluene.

18

19

20 Pd(acac)<sub>2</sub> was immobilized with an ionic ligand, which was generated *in situ* by  
21 protonation of 2-(dibutylphosphino)-*N,N*-dimethylethaneamine (Scheme 5.3-36).

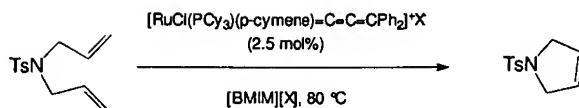
22 In this way a continuous dimerization was realized over 50 h time-on-stream  
23 producing  $\Delta^2$ -dihydrodimethylmuconate in an overall TON of more than 4000  
24 (product selectivity > 90%). This clearly demonstrates the potential of the biphasic  
25 ionic liquid system to bring the Pd-catalyzed MA dimerization closer to a technical  
26 realization.

27 By using scCO<sub>2</sub> instead of toluene as second phase, Pd-leaching could be avoided,  
28 even without additional ammoniumphosphine ligand and the TOF and selectivity  
29 was increased to 195 h<sup>-1</sup> and >98% respectively [253]. In another publication  
30 Tkachenko and coworkers demonstrated that the selective tail-to-tail dimerization  
31 of methyl acrylate can also be carried out with very good results in protonated *N*-  
32 butyl-imidazole, [HBIM][BF<sub>4</sub>], giving a first example of the versatility of such simple  
33 acid–base ionic liquids in continuous catalytic processes [254].

### 35 5.3.2.6 Olefin Metathesis

#### 36 *Ru-catalyzed ring-closing metathesis (RCM)*

37 The ability of ionic liquids to form miscibility gaps with many organic liquids  
38 has been the starting point for attempts to realize efficient catalyst recycling in  
39 liquid–liquid biphasic metathesis reactions. The field was pioneered by Bayer AG  
40 [255] and by Buijsman and coworkers [256]. The latter group reported, in 2001,  
41 that a solution of Grubbs Ru-catalyst complex (first generation) in [BMIM][PF<sub>6</sub>]  
42 promoted the ring-closing metathesis (RCM) of a number of different dienes for at  
43 least three catalytic cycles. However, catalytic performance decreased significantly  
44 over recycling which was attributed by the authors to catalyst leaching into the  
45 product phase.



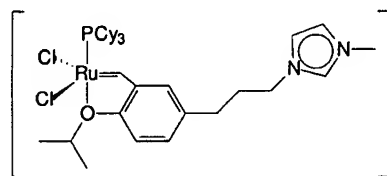
**Scheme 5.3-37** Ring-closing metathesis of diallyltosylamide catalyzed by a Grubbs first generation complex in  $[\text{BMIM}][\text{PF}_6]$ .

Slightly later, the ring-closing metathesis of diallylamides in 1-butyl-3-methylimidazolium salts using ruthenium allenylidene salts as catalyst precursors was reported by Olivier-Bourbigou and Dixneuf [257]. They realized a strong influence of the ionic liquid's anion on the catalytic performance with triflate ionic liquids showing the best performance. These observations are in good agreement with the known counter-ion sensitivity of the cationic ruthenium allenylidene complexes and suggest that effective anion exchange takes place in the ionic reaction medium. The RCM reaction of diallyltosylamide was reported to proceed in full conversion after 2.5 h at  $80^\circ\text{C}$  with 97% selectivity for the closed-ring product (Scheme 5.3-37).

However, they observed slow decomposition of the catalyst in the ionic liquid, behavior that was also observed in organic solvents. This decomposition prevented successful recycling of the ionic catalyst solution and significant loss of catalytic activity was already observed in the third cycle.

A Grubbs Ru-catalyst with a cationic, imidazolium based tag (Fig. 5.3-19) was prepared and evaluated by Mauduit and coworkers [258]. Again the test reaction was the RCM reaction of diallyltosylamide.

They reported full conversion in 45 min ( $60^\circ\text{C}$ ) with no cross-metathesis product being formed. Product extraction could be easily achieved with toluene and the ionic liquid catalyst solution was recycled nine times with conversions still exceeding 95% in the tenth cycle. The superior performance of the imidazolium-tagged catalyst in the recycling protocol was demonstrated by baseline runs with Grubbs and Hoveyda's catalyst in the same ionic liquid under identical conditions, both showing strong deactivation already in the first recycle. The obviously quite high catalyst stability of the imidazolium-tagged Ru-complex in  $[\text{BMIM}][\text{PF}_6]$  could be additionally demonstrated by the fact that the ionic catalyst solution could be stored for several months without loss of catalytic activity. A very similar strategy of



**Fig. 5.3-19** Imidazolium functionalized Ru-complex as used for the ring-closing metathesis of diallyltosylamide.

1 attaching a slightly different imidazolium tag to a Grubbs first generation catalyst  
2 was explored by Yao et al. using a broader set of substrates [259].

3 The same authors later expanded the concept and additionally provided an  
4 imidazolium-tagged Howeyda-Grubbs ruthenium carbene catalyst for the RCM  
5 reaction [260]. The resulting system proved to be highly active for the conversion of  
6 di-, tri- and tetrasubstituted diene and enyne substrates. In the catalyst solvent sys-  
7 tem [BMIM][PF<sub>6</sub>]-CH<sub>2</sub>Cl<sub>2</sub> (volume ratios: 1:1 to 1:9) the catalyst could be recycled  
8 17 times with only very slight loss in activity. Also in this work it was demon-  
9 strated that the imidazolium tag is essential to obtain a stable and recycleable  
10 catalyst.

11 The use of methylene chloride as cosolvent has to be seen as a drawback with  
12 regard to the "greenness" of the reaction protocol, even so the authors claim that its  
13 use minimizes the amount of ionic liquid volume and thus ionic liquid cost. The  
14 critical aspect of using methylene chloride was avoided by Mauduit et al. by using  
15 a [BMIM][PF<sub>6</sub>]/toluene and also a [BMIM][(CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>N]/toluene biphasic reaction  
16 system together with an imidazolium-tagged N-heterocyclic carbene ruthenium  
17 complex as the catalyst [261]. A high level of recyclability and reactivity could be  
18 achieved in the RCM reaction of several substrates including tri-substituted and  
19 oxygen-containing representatives. Only very low residual levels of ruthenium (1–22  
20 ppm) were detected in the products.

21 Finally, it should be mentioned here that Kiddle and coworkers have successfully  
22 carried out several RCM reactions in [BMIM][BF<sub>4</sub>] under microwave irradiation  
23 [262].

#### 24 25 26 *Ru-catalyzed self-cross-metathesis*

27 The self-cross metathesis (CM) of 1-octene to form 7-tetradecene catalyzed by sev-  
28 eral different Ru-carbene complexes (0.02 mol%) has been investigated by Williams  
29 and coworkers [263]. While the first generation Grubbs catalyst underwent rapid  
30 deactivation in both the applied ionic liquids (several imidazolium tetrafluorobo-  
31 rate, hexafluorophosphate and bis(trifluoromethylsulfonyl)imide salts), the second  
32 generation Grubbs catalyst showed significantly less secondary metathesis products  
33 in the ionic liquid compared to the reaction under identical conditions in organic  
34 solvents. Thus, in many cases very high selectivities (>98%) towards 7-tetradecene  
35 could be obtained in the ionic liquid media, even at very high 1-octene conversions  
36 (>95%).

37 Another comparative study of the CM reaction catalyzed by a second generation  
38 Grubbs carbene complex (without imidazolium tag) has been recently presented by  
39 Tang and coworkers [264]. They compared the catalytic transformation of styrene in  
40 [BMIM][BF<sub>4</sub>] and [BMIM][PF<sub>6</sub>] with the same reaction in CH<sub>2</sub>Cl<sub>2</sub> (3 h, 45 °C) and  
41 obtained comparable yields of the CM product in all solvents in the first cycle. In  
42 the case of the two ionic liquids the product was extracted with diethyl ether and the  
43 remaining ionic catalyst solution could be recycled four times with only a small drop  
44 in catalytic activity (product yield 75% in the fourth cycle compared to 85% in the first  
45 cycle in [BMIM][PF<sub>6</sub>]). The scope of the study also included the successful self-cross-



metathesis of *p*-methylstyrene, *p*-chlorostyrene,  $\alpha$ -methylstyrene and acrylonitrile in [BMIM][PF<sub>6</sub>] while some ether and amine functionalized olefins failed to react even after prolonged reaction times (12 h, 50 °C).

#### ***Ru-catalyzed ring-opening polymerization***

Ring-opening metathesis polymerization (ROMP) has also been successfully carried out in ionic liquids. Dixneuf and coworkers studied the biphasic ROMP reaction of norbornene in a 1-butyl-2,3-dimethylimidazolium hexafluorophosphate/toluene mixture using a ruthenium allenylidene pre-catalyst [265]. While the applied ionic liquid medium immobilized the cationic Ru-complex, the polymer formed during the reaction could be isolated in the toluene phase. The ionic catalyst solution was recycled successfully, however, reloading of the ionic liquid with a new portion of the Ru catalyst was necessary after 5 cycles to keep polymer yields high (for more details on polymerization reactions in ionic liquids see Chapter 7).

#### ***Tungsten and molybdenum catalyzed metathesis reactions***

Apart from Ru-catalyzed metathesis in ionic liquids two examples of tungsten catalyzed metathesis reactions have also been reported. Vasnev and coworkers studied the metathesis of 1-hexene catalyzed by WCl<sub>6</sub> in tetrafluoroborate ionic liquids [266]. In the reaction sequence under investigation, 1-hexene first isomerized to 2-hexene which then formed 4-octene and ethylene by cross-metathesis. The yields of the metathesis product were demonstrated to increase with increasing reaction temperature and with addition of a tin-containing promoter. 4-octene was obtained in selectivities up to 97% (at 25% 1-hexene conversion) when tetrabutyl tin was applied as the promoter in this reaction.

#### **5.3.2.7 Catalysis with Nanoparticulate Transition Metal Catalysts**

The scientific interest in catalysis by transition metal nanoparticles has seen a dramatic increase in recent years and significant progress has been made in improving selectivity, efficiency and recyclability of the catalytic systems [267]. Usually nanoparticulate catalysts are prepared from a metal salt, a reducing agent and a stabilizer and are supported on oxides, charcoal or zeolites.

Ionic liquids are quite unique media for the synthesis of nanoparticles. This perception has rapidly developed over the last three years and Section 6.3 of this book is devoted to the synthetic aspects of particle preparation in ionic liquids. Thus ionic liquids represent both innovative liquid support materials and stabilizers for catalytic reactions using transition metal nanoparticles.

In the context of this chapter we aim to illustrate the state-of-the-art in this rapidly progressing field of ionic liquid catalysis, exemplified for selective hydrogenation and Heck reactions. Other applications of nanoparticulate catalyst systems have been reported in hydrosilylation reactions [268], Suzuki [269] and Stille coupling [270].

### Hydrogenation reactions catalyzed by nanoparticulate transition metal catalysts

Catalytic hydrogenation reactions have to date been explored using nanoparticles of palladium, platinum, ruthenium, iridium and rhodium.

Pd nanoparticles (2–5 nm) have been obtained by Han and coworkers by reducing a solution of palladium acetate in [BMIM][PF<sub>6</sub>] with H<sub>2</sub> [271]. Phenanthroline was added to the reaction mixture to stabilize the nanoparticles. The suspension of the particles was applied to catalyse the hydrogenation of alkenes, and could be recycled several times without loss of activity. However, when the phenanthroline was omitted, the system severely lost its reactivity on the first recycle, presumably due to particle agglomeration. This gives an indication that the ionic liquid alone is not able to stabilize the nanoparticles in this system.

Han's group also reported the immobilization of Pd nanoparticles onto molecular sieves using 1,1,3,3-tetramethylguanidinium lactate as the ionic liquid [272]. In this case excellent synergistic effects between the nanoparticles, the ionic liquid and the molecular sieve support were reported, leading to a very active hydrogenation catalyst for the hydrogenation of 1-hexene and cyclohexene (TOF up to 66 min<sup>-1</sup> for 1-hexene hydrogenation).

Dupont's group later investigated the selective hydrogenation of 1,3-butadiene using Pd nanoparticles (particle size: 4.9 ± 0.8 nm) obtained from reduction of Pd(acac)<sub>2</sub> in [BMIM][PF<sub>6</sub>] or [BMIM][BF<sub>4</sub>] [273]. Selectivities to 1-butene of 72% could be achieved in this system at 99% butadiene conversion. The high selectivity to the partial hydrogenation product was attributed to the four times higher solubility of butadiene in the applied ionic liquid compared to the desired butanes. The lack of isomerization activity in the system was interpreted by the authors as an indication for a Pd-cluster surface reaction rather than a homogeneous reaction caused by Pd-complexes leached from the surface.

In this context we recall the fact that the 1,3-dialkylimidazolium ion is not innocent vs. Pd(0) and the ionic liquid's cation may convert into a carbene ligand, especially when catalysis is carried out at higher temperatures. Carbene ligands formed in this way can either be bound to the nanoparticle surface or form mononuclear carbene complexes with metal atoms leached from the nanoparticle's surface [267b].

Dupont and coworkers obtained Pt nanoparticles (2–2.5 nm) in [BMIM][PF<sub>6</sub>] by reducing dissolved Pt<sub>2</sub>(dba)<sub>3</sub> with H<sub>2</sub> (4 atm) at 75 °C [274]. The formed nanoparticles catalyzed the hydrogenation of both alkenes and arenes under the same, relatively mild conditions. However, the ionic liquid suspension gave a less active catalytic system (lower TOF) compared to the same particles under solventless conditions or in acetone. The generated Pt(0) nanoparticles were found to be quite stable and could be re-used, as solid, or re-dispersed in [BMIM][PF<sub>6</sub>] several times with little loss of catalytic activity.

Ru nanoparticles have also been prepared in ionic liquids and used for catalytic hydrogenation reactions. Dupont's group described the reduction of RuO<sub>2</sub> with hydrogen in different ionic liquids with the [BMIM] cation [275]. The Ru nanoparticles were characterized by TEM and XRD and were 2.0–2.5 nm in diameter with a narrow size distribution. The authors demonstrated that the particles dispersed in the ionic liquid were less prone to oxidation compared to isolated nanoparticles.

1 The Ru nanoparticles in [BMIM][PF<sub>6</sub>] proved to form a very stable catalytic system  
2 for the hydrogenation of 1-hexene with turnover numbers of 110000 (based on total  
3 Ru) or 320000 (based on Ru surface atoms) being obtained over 17 recycles of the  
4 catalyst system. These authors also investigated the reduction of RuO<sub>2</sub> dissolved in  
5 [BMIM][PF<sub>6</sub>] with Na[BH<sub>4</sub>] and also obtained a highly active catalytic system of ionic  
6 liquid supported Ru nanoparticles which was successfully applied in the hydrogenation  
7 of olefins under mild conditions [276]. In another publication, Dupont's group  
8 described an optimized benzene hydrogenation protocol using Ru nanoparticles in  
9 ionic liquids to obtain the partial hydrogenation product cyclohexene [277]. Making  
10 use of the preferential solubility of benzene compared to cyclohexene in the ionic  
11 liquid [BMIM][PF<sub>6</sub>] these authors were able to realize selectivities to cyclohexene of  
12 up to 39%, however this high selectivity was only realized at low benzene conversion  
13 with only a 2% yield of cyclohexene.

14 A solid supported form of Ru nanoparticles in ionic liquids was again introduced  
15 by Han and coworkers [278]. They applied 1,1,3,3-tetramethylguanidinium([TGA])-  
16 exchanged Montmorillonite – naturally occurring, negatively charged two-  
17 dimensional silicate sheets separated by interlayers of [TGA] ions – as a supporting  
18 and stabilizing medium for the Ru nanoparticles. The favorable synergistic effects  
19 of the [TMG] ions, the Montmorillonite support and the Ru particles led to a catalytic  
20 material exhibiting high activity in benzene hydrogenation (TOF = 4000 h<sup>-1</sup>) and  
21 excellent stability.

22 Finally, a very interesting approach has been suggested by the same group to apply  
23 an ionic liquid to the preparation of Ru nanoparticles of defined size on a meso-  
24 porous silica support [279]. The authors made use of the ionic liquid [TGA][lactate]  
25 to customize particles obtained by reduction of dissolved RuCl<sub>3</sub> on the silica sup-  
26 port. However, prior to catalysis, the ionic liquid film was removed thermally by  
27 heating to 220 °C for 3 h. In this way a quite active catalyst for the hydrogenation  
28 of benzene to cyclohexane (TOFs up to 83 h<sup>-1</sup> at 10 bar H<sub>2</sub> pressure) was obtained.  
29 Such an approach obviously combines successfully features of SILP catalysis (see  
30 Section 5.6 for details) with the use of catalytic nanoparticles.

31 Iridium and rhodium nanoparticles have also been used as hydrogenation cat-  
32 alysts, suspended in [BMIM][PF<sub>6</sub>] [280]. The nanoparticles were precipitated from  
33 solutions of RhCl<sub>3</sub>·3H<sub>2</sub>O or [Ir(COD)Cl]<sub>2</sub> by applying H<sub>2</sub> (4 atm) at 75 °C, giving  
34 particles of mean diameter 2.3 nm and 2.1 nm, respectively. The nanoparticles  
35 were used to hydrogenate benzene, but in both cases were less reactive than the  
36 same nanoparticles under either solventless conditions or in acetone. The iridium  
37 particles remained unchanged by reaction, whereas the rhodium particles clearly  
38 agglomerated. An approach to prevent this particle agglomeration was presented  
39 later by Kou and coworkers [281]. They applied ionic liquid–soluble ionic copoly-  
40 mers containing imidazolium moieties to successfully stabilize Rh nanoparticles in  
41 [BMIM][BF<sub>4</sub>] and thus reached unprecedented catalytic lifetime and activity (total  
42 turnover number of 20000 obtained in four recycles) of the particles in benzene  
43 hydrogenation under relatively harsh conditions (75 °C, 40 bar H<sub>2</sub>). Ir nanoparti-  
44 cles have also been applied to catalyze the hydrogenation of various ketones to the  
45 corresponding alcohols [84]. Particles of 2.3 ± 0.4 nm were obtained by reduction

of  $[\text{Ir}(\text{cod})\text{Cl}]_2$  in  $[\text{BMIM}][\text{PF}_6]$  and showed a turnover frequency of  $208 \text{ h}^{-1}$  in the reduction of cyclohexanone to cyclohexanol ( $75^\circ\text{C}$ ; 6 bar  $\text{H}_2$ ).

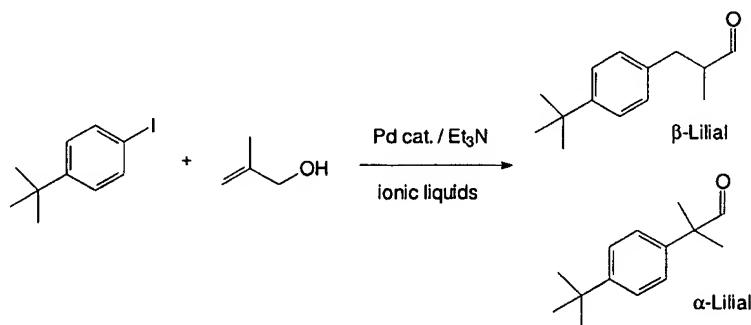
It should be noted, that the examples of nanoparticulate hydrogenation catalysis in ionic liquids presented here do not represent the full list of successful, published applications. Several other groups have recently contributed details on the formation, stabilization and immobilization of nanoparticles in ionic liquids and have described the catalytic activity and reaction kinetics of these systems in different hydrogenation reactions [282].

#### Heck reaction catalyzed by nanoparticulate catalysts

An early account of the role of Pd nanoparticles in the Heck reaction was published by Srinivasan and coworkers in 2001 [283]. They carried out Heck reactions of different aryl iodides with acrylates and styrene at ambient temperature and observed a significant rate enhancement by combining ultrasonic irradiation with the use of the ionic liquid 1,3-dibutylimidazolium tetrafluoroborate as the reaction medium. Under the sonochemical conditions the formation of Pd–biscarbene complexes was observed and these later transformed into Pd nanoparticles.

In a study dealing with the Heck arylation of 2-methyl-prop-2-en-1-ol and 1-*tert*-butyl-4-iodobenzene to obtain the fragrance  $\beta$ -Lilial, Seddon and coworkers have studied several homogeneous and heterogeneous Pd catalysts in bromide and bis(trifluoromethylsulfon)imide ionic liquids (Scheme 5.3-38) [284]. Induction periods of the catalyst – for both Pd/C and for  $[\text{Pd}(\text{btz})_2\text{I}_2]$  – were observed and associated by the authors with the formation of Pd nanoparticles in solution.

Calo et al. reported that, in the presence of tetrabutylammonium acetate as base, a palladium complex with benzothiazolidene as ligands as well as palladium acetate is transformed to Pd nanoparticles which catalyze regio- and stereo-specific Heck reactions [285]. The same authors have also applied the complex  $[\text{PdI}_2(\text{C}_1\text{bth})_2]$  ( $\text{C}_1\text{bth}$  = methylbenzthiazolydene, Fig. 5.3-20) as a source of palladium in  $[\text{Bu}_4\text{N}]\text{Br}$ , with no added ligands [286]. In this case, they have identified the formation of nanoparticles



Scheme 5.3-38 Heck arylation of 2-methyl-prop-2-en-1-ol and 1-*tert*-butyl-4-iodobenzene for the synthesis of  $\beta$ -Lilial.

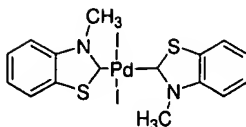


Fig. 5.3-20 Bis(methylbenzthiazolylidene)palladium diiodide.

of 2–6 nm diameter which are responsible for the catalytic activity in the reaction of cinnamates with aryl halides to give  $\beta$ -aryl-substituted cinammic esters. The presence of tetrabutylammonium acetate was found to be crucial for the formation of the nanoparticles.

Calo and coworkers have also studied the regioselectivity of Pd-nanoparticle catalyzed Heck arylations using aryl bromide and the 1,1-disubstituted olefins butyl methylacrylate and  $\alpha$ -methylstyrene as the reactants in tetrabutylammonium bromide as the reaction medium and with tetrabutylammonium acetate as the base [287].

Dupont et al. immobilized Pd(0) nanoparticles in [BMIM][PF<sub>6</sub>] and observed for the coupling of aryl halides with butyl acrylate that the size of the particles increased over reaction [288]. They also described significant metal leaching (up to 34%) from the ionic phase to the organic phase at low substrate conversions, which dropped to 5–8% leaching at higher conversions. These results strongly suggest that the Pd(0) nanoparticles served as reservoir for a homogeneous catalytic active species in this case.

An immobilized version of a Heck reaction catalyzed by Pd nanoparticles has been very recently described by Karimi and Enders [289]. The nanoparticles were obtained as a result of the covalent anchoring of a N-heterocyclic carbene palladium/ionic liquid matrix on a silica surface and their nature was confirmed by TEM coupled with EDX analysis. The catalyst showed high thermal stability (up to 280 °C) and could be recycled four times for the reaction of bromobenzene with methylacrylate achieving a total turnover number of 36600. After carrying out a hot filtration process, the authors could not detect any Pd in the filtrate. The filtrate also showed no further reaction progress. From these findings the authors concluded that the reaction was, in their case, indeed catalyzed by the heterogeneous Pd particles and not from monomolecular Pd-complexes leached from the surface.

### 5.3.3

#### Concluding Remarks: “Low-hanging Fruits” and “High-hanging Fruits” – Which Transition Metal Catalyzed Reaction Should Be Carried Out in an Ionic Liquid?

Obviously, there are many good reasons to study ionic liquids as alternative solvents in transition metal catalyzed reactions. Besides the engineering advantage of their non-volatile nature, the investigation of new biphasic reactions with an ionic catalyst phase is of special interest. The possibility of adjusting solubility properties by different cation/anion combinations allows a systematic optimization of the

1 biphasic reaction (e.g., with regard to product selectivity). Attractive options to im-  
2 prove selectivity in multiphase reactions derive from the preferential solubility of  
3 only one reactant in the catalyst solvent or from the *in situ* extraction of reaction  
4 intermediates out of the catalyst layer. Moreover, the application of an ionic liquid  
5 catalyst layer enables a biphasic reaction mode in many cases where this is not  
6 possible using water or polar organic solvents (e.g., due to incompatibility with the  
7 catalyst or problems with substrate solubility).

8 However, the concept of using ionic liquids in transition metal catalysis brings  
9 along some general features that have to do with the general properties of ionic  
10 liquids. In the last three years we have learned a lot more about ionic liquids and  
11 we have realized that despite some properties of ionic liquids being tuneable over a  
12 wide range, others are more or less intrinsic to the approach. In the light of such a  
13 property profile it may be a valuable exercise to evaluate in general terms different  
14 applications of transition metal catalysis with regard to their fit to this property  
15 profile. Such an evaluation may help to estimate the research effort required and  
16 the time to success that has to be expected. It also may give an indication at which  
17 point additional fundamental research is necessary to make an envisaged transition  
18 metal-mediated reaction or process a success.

19 What are the criteria that have to be considered in such an evaluation process?  
20 In the following paragraphs we have tried to condense our more than ten years of  
21 experience in transition metal catalysis in ionic liquids into a five-point check list  
22 that is hopefully helpful in this context.

#### 23 24 ***Ionic liquid stability under process conditions***

25 A first very important and far from trivial point is ionic liquid stability under the  
26 conditions required for the catalytic application under investigation. This point  
27 becomes especially interesting given the fact that in far the most cases the process  
28 development will aim for an extensive ionic liquid recycling, which naturally implies  
29 special requests for long term stability issues.

30 Ionic liquid stability is known to be a function of temperature (for details see  
31 Section 3.1) but the presence of nucleophiles/bases and the water content also have  
32 to be considered. There is no doubt that, under the conditions of a catalytic reaction,  
33 temperature stability issues are more complicated than under the conditions  
34 of a TGA experiment. The presence of the catalyst complex, the reactants and  
35 impurities in the system may well influence the thermal stability of the ionic  
36 liquid. Basic and nucleophilic counter-ions, reactants and metal complexes may  
37 not only lead to deprotonation of 1,3-dialkylimidazolium ions (to form carbene  
38 moieties that will undergo further consecutive reactions) but will also promote  
39 thermal dealkylation of the ionic liquid's cation. If basic reaction conditions are  
40 required for the catalysis only tetraalkylphosphonium ions can be recommended  
41 as the ionic liquid's cation at this point in time. Tetraalkylphosphonium cations  
42 have been recently shown to display reasonable stability, even under strongly basic  
43 conditions [290]. In contrast, all nitrogen-based cations suffer to some extent from  
44 either carbene formation, Hofmann elimination or rapid dealkylation (with alkyl  
45 transfer onto the nucleophilic anion).

Water is likely to be present in all practically relevant catalytic applications unless extreme precautions are taken or the system is self-drying (e.g., due to the fact that strong Lewis-acids or metal alkyls are used as co-catalysts). Water will influence the ionic liquid's thermal stability significantly if any part of the ionic liquid is prone to hydrolysis. Apart from the well-known hydrolysis lability of tetrafluoroborates and hexafluorophosphates, water will thus also affect the stability of ester functionalities in the ionic liquid, e.g. the stability of alkyl sulfate anions. The presence of Brønsted acidity in the reaction system will further promote this kind of thermally induced hydrolysis reaction. Additionally, in strong Lewis-acidic ionic liquids care has to be taken to avoid incompatibilities between oxygen and nitrogen functionalities in the reactants or impurities and the ionic liquid's Lewis acidic group (usually a complex anion). It is for example obvious that the Pd-catalyzed dimerization of methylacrylate cannot be carried out in acidic chloroaluminate ionic liquids since the ionic liquid's anion would decompose in an irreversible reaction with the substrate methylacrylate.

Taking all these aspects into account and trying to come to a general view of the thermal stability of ionic liquids in catalytic processes we can safely state today that the chance to identify a sufficient thermally stable ionic liquid for transition metal catalysis is quite realistic if the temperature does not exceed 180 °C. This, by the way, is also the temperature limit encountered for the stability of most organometallic transition metal complexes used in homogeneous catalysis. The latter consideration somehow relativizes the restrictions imposed by the limited thermal stability of many ionic liquids for the specific application of transition metal catalysis.

#### ***Catalyst solubility in the ionic liquid without deactivation***

In many cases, catalyst solubility is not a strong concern for transition metal catalysis in ionic liquids. Most transition metal complexes are polarisable enough to be well soluble in most ionic liquids. However, it is important to consider the ability of the ionic liquid to interact with the coordination sites of the metal complexes involved in the catalytic cycle.

In a general (and generalizing) view on this issue it can be stated that suitably selected ionic liquids are very likely to form catalytically active ionic catalyst solutions with a given transition metal catalyst if the latter is neither extremely electrophilic (acidic) nor extremely nucleophilic (basic). While extremely electrophilic catalyst complexes are likely to coordinate strongly even with those anions of the ionic liquid solvent which are generally regarded as weakly coordinating, extremely nucleophilic catalytic centers are likely to react with the ionic liquid's cation. Carbene complex formation by oxidative addition as well as dealkylation of the cation are possible deactivation pathways of the catalyst in such a case.

#### ***Feedstock concentration in the ionic catalyst solution***

Usually, the rate of a catalytic reaction depends on the concentration of the reactants in a positive reaction order. Thus, the rate of the catalytic reaction increases if a higher concentration of the feedstock is available in the catalyst phase. As mentioned earlier (see Section 5.3.1.2) the available feedstock concentration depends,

## 450 | 5 Organic Synthesis

1 in multiphasic catalysis, on both the thermodynamic equilibrium solubility of the  
2 reactant in the ionic liquid and on the mass transfer rate of the reactant into the  
3 ionic reaction medium.

4 To evaluate *a priori* whether mass transfer or solubility issues will seriously  
5 affect the probability for success in multiphasic ionic liquid catalysis the following  
6 considerations may be valuable.

7 It should be checked first whether solubility data for the reactants of the envisaged  
8 reactions in any ionic liquid are available. Special attention should be given to the  
9 solubility of gaseous reactants. These solubilities might be strongly dependent on  
10 temperature and pressure (see Section 3.4 for details). If the solubility of one reactant  
11 appears very low the ionic liquid's structure should be selected so as to maximize  
12 the solubility of this reactant.

13 Potential limitations by mass transfer issues become more likely if the reactivity  
14 of the transition metal complex in the ionic liquid is high (thus quickly converting  
15 all reactant entering the catalytic phase), the size of the reactant is large and the  
16 viscosity of the ionic liquid under the reaction conditions is high (diffusion coeffi-  
17 cients become small for the diffusion of big molecules into highly viscous media).  
18 Therefore the application of low viscosity ionic liquids is particularly advisable if the  
19 catalyst complex dissolved in the ionic liquid is likely to be highly active.

21  
22 **Product isolation**

23 Since ionic liquids have no vapor pressure, one of the usual methods of product iso-  
24 lation, evaporation of the solvent, is not an option. The product isolation techniques  
25 available are distillation/sublimation of the product from the ionic liquid, precipi-  
26 tation of the product and extraction of the product into another solvent. In the latter  
27 case it is often imperative to have the product soluble in an extracting solvent but  
28 the catalyst still well immobilized in the ionic liquid, so that the catalyst remains in  
29 the ionic liquid phase. This prevents the need for subsequent purification steps to  
30 remove the catalyst from the product. In many situations, e.g. in cases where solid  
31 reactants have only limited solubility in the ionic liquid, it is preferable to have the  
32 extracting solvent already present during the reaction.

33 In an attempt to predict whether product isolation will be trivial or will be a major  
34 problem for an envisaged application of transition metal catalysis in ionic liquids  
35 Fig. 5.3-21 has been designed. Here, we have grouped the different established tech-  
36 niques of product isolation from ionic liquids in the order of increasing operating  
37 effort. Obviously, the classification is strongly related to specific product properties  
38 making certain groups of products much more easily recoverable from ionic catalyst  
39 solutions than others.

40 From these considerations it is quite clear that applications that require a compli-  
41 cated and costly separation technique (near the top in Fig. 5.3-21) need to justify the  
42 use of the ionic liquid technique with great advantages in the reaction step. Only for  
43 quite exciting and somehow unique chemistry found in ionic liquids may the appli-  
44 cation of specific membrane separation techniques [291] or even the development  
45 of fundamentally new separation techniques be justified.



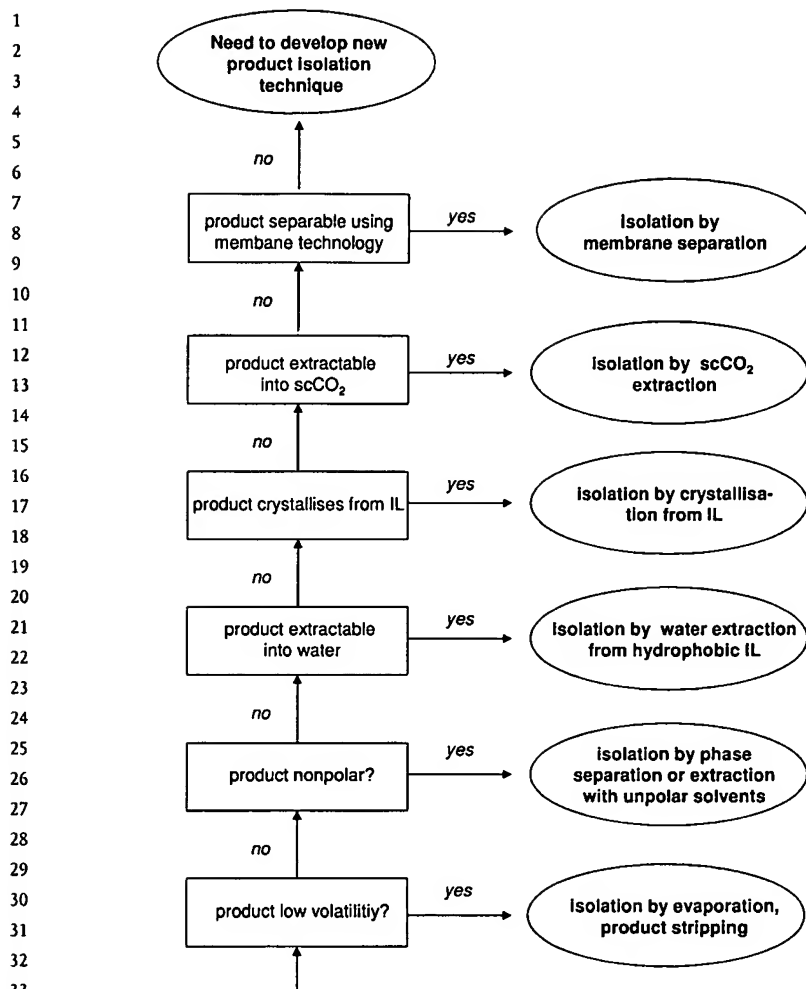


Fig. 5.3-21 Work-up options for transition metal catalysis in ionic liquids.

#### Recyclability and processability

Let us first make a very general but nevertheless very true and important statement: One should never try to immobilize and recycle a bad catalyst. That in particular is true for catalyst immobilization in ionic liquids.

“Bad” may mean in some cases that the catalyst does not meet the activity or selectivity criteria to justify any recycling effort in the frame of a process development scheme. “Bad” may mean in other cases that a very selective and also initially quite active catalyst shows poor long-term stability. Obviously, one can easily waste a lot of time in immobilizing an intrinsically unstable catalyst complex in an ionic liquid. However, this work will always result in the frustrating recovery of catalytically

## 452 | 5 Organic Synthesis

1 inactive ionic liquid (containing the catalyst degradation products). Exceptions to  
2 this general rule may arise if the ionic liquid shows significant stabilizing effect  
3 for the active catalytic species. Without doubt, it is much more advisable in such  
4 a scenario to focus development resources on exploring potential stabilizing ionic  
5 liquid – catalyst interactions rather than trying to fight metal leaching into the  
6 organic phase.

7 Once a very stable ionic catalyst solution that shows all required selectivity and  
8 production rate characteristics has been identified, metal leaching into the product  
9 phase is indeed the next issue that has to be addressed. Excellent advances have been  
10 made in recent years in this field. In many applications it was possible to suppress  
11 catalyst leaching down to ppb levels using ionic ligands attached to the catalytic  
12 metal (see this section and Section 5.4 for numerous examples). Another strategy  
13 that very effectively avoids leaching problems is to isolate the reaction products from  
14 the ionic catalyst solution via the gas phase. This approach has been very effectively  
15 realized in the SILP catalysis technique (see Section 5.6 for details) and builds on  
16 the extremely low volatility of transition metal complexes dissolved in ionic liquids.

17 When it finally comes to continuous processing of transition metal catalysis in  
18 ionic liquid–organic biphasic reaction mode, some additional aspects have to be  
19 taken into account. First is the ease of phase separation that will determine the size  
20 of the separator unit and thus indirectly the ionic liquid hold-up required. Another  
21 very important aspect is the build-up of side-products or feedstock impurities in the  
22 ionic catalyst phase. Side-products and impurities that are likely to build up in the  
23 ionic liquid are relatively polar in nature and this brings along a significant risk of  
24 unfavorable interactions with the transition metal catalyst complex. Apart from this,  
25 all build-up of undesired components in the ionic liquid will also affect the ionic  
26 liquid's physicochemical properties. Therefore, a continuous build-up of compo-  
27 nents in the ionic catalyst phase that is not restricted by thermodynamic limits (e.g.  
28 solubility limits) will always require an extensive purge of the ionic catalyst solution.

29 It was our intention to discuss in this last and concluding part of our section  
30 the *a priori* evaluation of the chances and risks of an envisaged research project in  
31 transition metal catalysis using ionic liquids. If all five critical issues that have been  
32 discussed above can be answered in favor of the ionic liquid concept, a successful and  
33 rapid development is probable and existing separation technologies, known ionic  
34 liquids and established reactor concepts are likely to work. It can be expected in these  
35 cases that the specific properties of ionic liquids will fit the specific application very  
36 convincingly and, therefore, application of the ionic liquid technology might well  
37 be superior compared to the state of the art. In these cases, it can be anticipated  
38 that successful and very product focused research is possible without the need for  
39 further development of the ionic liquid methodology itself.

40 In contrast, additional and more or less fundamental work is necessary if one or  
41 more of the named aspects are unfavorable to the envisaged concept. Optimized  
42 ionic liquid structures, new transition metal complexes and/or a different separation  
43 concept might have to be developed in these cases. We do not want to discourage  
44 anybody from trying to apply ionic liquids in those reactions also but at least a  
45 significantly lower success rate and a significantly longer time to success has to be

expected. But, high hanging fruits are usually sweetest and harvesting one of them may justify in the end all the extra effort that was necessary to get there.

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## 454 | 5 Organic Synthesis

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## 5-4 Ionic Liquids in Multiphasic Reactions

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### 5.4.1

#### Multiphasic Reactions: General Features, Scope and Limitations

While the solubility of organometallic complexes in common organic solvents appears to be an advantage in terms of site availability and tunability and reaction selectivity and activity, it is a major drawback in terms of catalyst separation and recycling. The quest for new catalyst immobilization or recovery strategies to facilitate its reuse is unceasing. Immobilization of the catalyst on a solid support has been largely studied. Except for Ziegler-Natta and metallocene-type polymerization processes, in which the catalyst is not recycled due to its high activity, this technology has not been developed industrially, mainly because of problems of catalyst leaching and deactivation. One most successful approach to close the advantage/disadvantage gap between homogeneous and heterogeneous catalysis is multiphasic catalysis [1]. In its simplest version, there are only two liquid phases (biphasic catalysis or two-phase catalysis). The catalyst is dissolved in one phase (generally a polar phase) while the products and the substrates are found in the other. The catalyst can be separated by decantation and recycled under mild conditions.

It is important to make the distinction between the multiphasic catalysis concept and transfer-assisted organometallic reactions or phase transfer catalysis (PTC). In this latter approach, a catalytic amount of quaternary ammonium salt  $[Q]^+[X]^-$  is present in an aqueous phase. The catalyst lipophilic cation  $[Q]^+$  transports the reactant's anion  $Y^-$  to the organic phase, as an ion-pair, and the chemical reaction occurs in the organic phase of the organic/aqueous two-phase mixture [2].

The use of multiphasic catalysis has proven its potential in important industrial processes. In 1977, the first large-scale commercial catalytic process to benefit from two-phase liquid/liquid technology was the Shell Higher Olefin Process (SHOP) for oligomerization of ethene into  $\alpha$ -olefins, catalyzed by nickel complexes dissolved in diols such as 1,4-butanediol. Subsequently, the advancement in two-phase homogeneous catalysis has been demonstrated by the biphasic aqueous hydroformylation as an economically competitive large-scale process. The first commercial oxo plant, developed by Ruhrchemie-Rhône-Poulenc for the production of butyraldehyde from propene, came on stream in 1984. This is an example of a gas-liquid-liquid multiphasic system in which the homogeneous rhodium-based catalyst is immobilized in a water phase by coordination to the hydrophilic trisulfonated triphenylphosphine ligand (TPPTS) [3]. The catalyst separation is more effective and simpler than in classical rhodium processes, but separation of by-products from the catalyst is also an important issue.

Since then, water has emerged as a useful solvent for organometallic catalysis. In addition to the hydroformylation reactions, several other industrial processes employing homogeneous catalysis have been converted to aqueous-phase procedures [4].

#### 5.4.2

#### Multiphasic Catalysis: Limitations and Challenges

Multiphasic (biphasic) catalysis relies on the transfer of organic substrates into the catalyst phase or on catalysis at the phase boundary. Most organic substrates do not have sufficient solubility in the catalyst phase (particularly in water) to give practical reaction rates in catalytic applications. Therefore, although the use of aqueous-biphasic catalysis has proven its potential in important industrial processes, the current applications of this technique remain limited: first to catalysts that are stable in the presence of water, and secondly to substrates that have significant water solubility. Many studies have focused on improving the affinities between the two liquid aqueous/organic phases, either through increasing the lipophilic character of the catalyst phase or even by immobilizing the catalyst on a support. For example, rapid stirring, emulsification, and sonication have been used to increase the interfacial area. The addition of co-solvents to the aqueous phase has been investigated extensively as a means of improving the solubility of higher olefinic substrates in the catalyst-containing phase. Application of detergents or micellar processes promoting the substrate transfer to the interface or the addition of co-ligands such as  $\text{PPh}_3$  – or even ligands with an amphiphilic character, or modified cyclodextrins – also play rate-enhancing roles. The development of supported aqueous-phase catalysis (SAPC) which involves the dissolution of an aqueous-phase complex on a thin layer of water adhering to a silica surface, opens the way to the reactivity of hydrophobic substrates. Although all these techniques can change the solubility of organic substrates in the aqueous phase or favor the concentration of the active center at the interface, they can also cause leaching of a proportion of the catalyst into the organic phase.

The major advantage of the use of two-phase catalysis is the easy separation of the catalyst and product phases. However, the co-miscibility of the product and catalyst phases can be problematic. An example is given by the biphasic aqueous hydroformylation of ethene to propanal. First, the propanal formed contains water, which has to be removed by distillation. This is difficult due to formation of azeotropic mixtures. Secondly, a significant proportion of rhodium catalyst is extracted from the reactor with the products, which prevents its efficient recovery. Nevertheless the reaction of ethene itself in the water-based Rh-TPPTS system is fast. It is the high solubility of water in the propanal that prevents the application of the aqueous biphasic process [5].

To overcome these limitations, there has been much investigation of novel methods, one of them focused on the search for alternative solvents [6,7]. Table 5.4-1 lists

different approaches of biphasic catalysis, with some of their respective advantages and limitations.

Although already well-known, perfluorinated solvents have only quite recently proved their utility in many organic and catalyzed reactions. The main advantage of these solvents is that their miscibility with organic products can be tuned by varying the temperature. Fluorous-phase catalysis makes possible the association of homogeneous phase catalysis (thus avoiding problems of mass-transfer limitations) and a biphasic separation of the catalyst and reaction mixture [8]. However, these solvents are still relatively expensive and require costly, specially designed, ligands to keep the catalyst in the fluorous phase during the separation. In addition, a significant amount of perfluorinated solvent can remain dissolved in the organic phase, and contamination of the products can occur. To date, there are no industrial developments of this technology, due to the lack of competitiveness.

Supercritical carbon dioxide ( $\text{ScCO}_2$ ) has also emerged as a highly promising reaction medium. In combination with homogeneous catalysis, its benefits could be the potential increase in the reaction rates (absence of gas–liquid phase boundary, high diffusion rates) and selectivities, and also lack of toxicity [9]. In combination with water, it has been used in a biphasic system to perform the hydrogenation of cinnamaldehyde. Gas–liquid–liquid mass transfer limitations were ruled out, due to the very high solubility of reactant gas in  $\text{ScCO}_2$  [10]. Although elegant, this approach still appears relatively expensive, especially for the bulk chemical industry. Furthermore, the low solubility of interesting substrates may hamper the commercialization of  $\text{ScCO}_2$  in the fine chemical industry. A very recent and highly interesting development is the combination of an ionic liquid catalyst phase and a product phase containing  $\text{scCO}_2$ . This approach is presented in more detail in Section 5.7.

Further progress in multiphasic catalysis will rely on the development of alternative techniques that allow the reactivity of a broader range of substrates, the efficient separation of the products, and recovery of the catalyst, while remaining economically viable.

#### 5.4.3

##### Why Ionic Liquids in Multiphasic Catalysis?

Notwithstanding their very low vapor pressure, their good thermal stability (for thermal decomposition temperatures of several ionic liquids see Refs. [11, 12]) and their wide operating range, the key property of ionic liquids is the potential to tune their physical and chemical properties by varying the nature of the anions and cations. An illustration of their versatility is given by their exceptional solubility characteristics, which make them good candidates for multiphasic reactions (see Section 3.3). Their miscibility with water, for example, depends not only on the hydrophobicity of the cation, but also on the nature of the anion and on the temperature.

$N,N'$ -Dialkylimidazolium cations are of particular interest because they generally give low melting salts, are more thermally stable than their tetraalkylammonium

Table 5.4-1 Advantages and limitations of different approaches for multiphasic "homogeneous" catalysis

Catalyst phase	Product phase	Advantages	Limitations
Water (+co-solvent)	Organic liquid	<ul style="list-style-type: none"> <li>• Easy product separation and catalyst recycling</li> <li>• Lower cost of chemical processes</li> <li>• Lack of toxicity of water</li> </ul>	<ul style="list-style-type: none"> <li>• Low reaction rate for water poorly miscible substrates</li> <li>• Mass transfer limits rate of reaction</li> <li>• Treatment of spent water</li> </ul>
Polar solvent	Organic liquid	<ul style="list-style-type: none"> <li>• Solvent effect</li> </ul>	<ul style="list-style-type: none"> <li>• Use of volatile organic solvent</li> <li>• Co-miscibility of the two phases</li> </ul>
Fluorinated organic solvent	Organic liquid	<ul style="list-style-type: none"> <li>• Temperature dependence of the miscibility of fluorinated phase with organic solvents</li> </ul>	<ul style="list-style-type: none"> <li>• Solvent and ligand costs</li> <li>• Product contamination</li> </ul>
Water	Supercritical fluids (e.g. CO <sub>2</sub> )	<ul style="list-style-type: none"> <li>• Organic co-solvent not needed</li> <li>• High miscibility of CO<sub>2</sub> with gas</li> </ul>	<ul style="list-style-type: none"> <li>• Poor solvating ability of supercritical fluids</li> <li>• High investment and operating costs</li> </ul>
Ionic liquid	Organic liquid	<ul style="list-style-type: none"> <li>• Tunability of the solubility characteristics of the ionic liquids</li> <li>• Solvent effect</li> </ul>	<ul style="list-style-type: none"> <li>• Ionic liquid costs</li> <li>• Disposal of spent ionic liquids</li> </ul>
Ionic liquid	Supercritical fluids (e.g. CO <sub>2</sub> )	<ul style="list-style-type: none"> <li>• Organic co-solvent not needed</li> <li>• Tunability of the solubility characteristics of the ionic liquids</li> <li>• Presence of CO<sub>2</sub> reduces ionic liquid's viscosity</li> </ul>	<ul style="list-style-type: none"> <li>• Ionic liquid costs</li> <li>• High pressure apparatus needed</li> </ul>



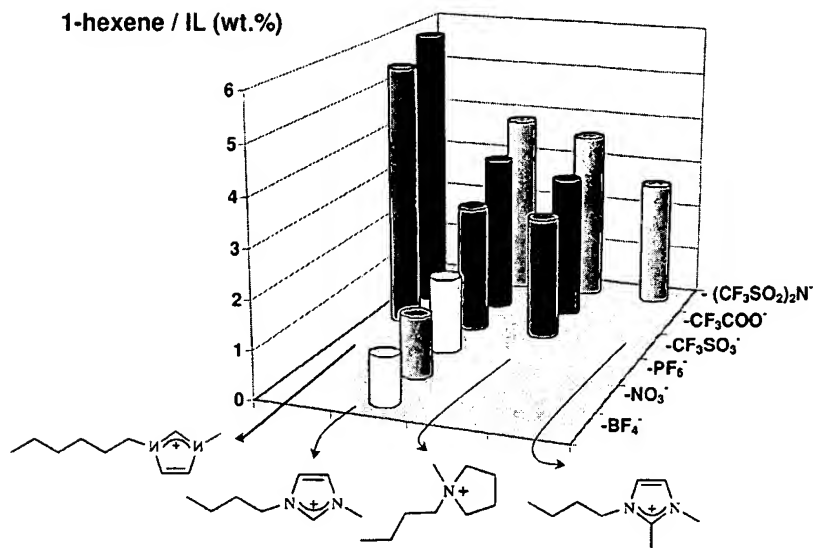


Fig. 5.4-1 Solubility of 1-hexene in different ionic liquids as a function of the nature of the anions and cations.

analogues, and have a wide spectrum of physicochemical properties available. For the same [BMIM]<sup>+</sup> cation, the [BF<sub>4</sub>]<sup>-</sup>, [CF<sub>3</sub>SO<sub>3</sub>]<sup>-</sup>, [CF<sub>3</sub>CO<sub>2</sub>]<sup>-</sup>, [NO<sub>3</sub>]<sup>-</sup>, and halide salts display a complete miscibility with water at 25 °C. On cooling the [BMIM][BF<sub>4</sub>]/water solution to 4 °C, however, a water-rich phase separates. Similarly, changing the [BMIM]<sup>+</sup> cation to the longer chain, more hydrophobic [HMIM]<sup>+</sup> (1-hexyl-3-methylimidazolium) cation affords a BF<sub>4</sub><sup>-</sup> salt that shows low co-miscibility with water at room temperature. On the other hand, the [BMIM][PF<sub>6</sub>], [BMIM][SbF<sub>6</sub>], [BMIM][NTf<sub>2</sub>] (NTf<sub>2</sub> = N(CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>) and [BMIM][BR<sub>4</sub>] ionic liquids show a very low miscibility with water, but the shorter, symmetrically substituted, [MMIM][PF<sub>6</sub>] salt becomes water soluble. One might therefore expect that modification of the alkyl substituents of the imidazolium ring could produce different and very tunable ionic liquid properties.

The influence of the nature of cations and anions on the solubility characteristics of the resulting salts with organic substrates is also discussed in Section 3.3. It has been shown (Fig. 5.4-1) that increasing the length of the alkyl chain on the imidazolium cation can increase the solubility of 1-hexene, but so can tuning the nature of the anion.

A comparison of the solubility of  $\alpha$ -olefins with increasing numbers of carbon atoms in water and in [BMIM][BF<sub>4</sub>] (Fig. 5.4-2), shows that olefins are at least 100 times more soluble in ionic liquids than in water.

Addition of co-solvents can also change the co-miscibility characteristics of ionic liquids. As an example, the hydrophobic [BMIM][PF<sub>6</sub>] salt can be completely dissolved in an aqueous-ethanol mixture containing between 0.5 and 0.9 mole fraction

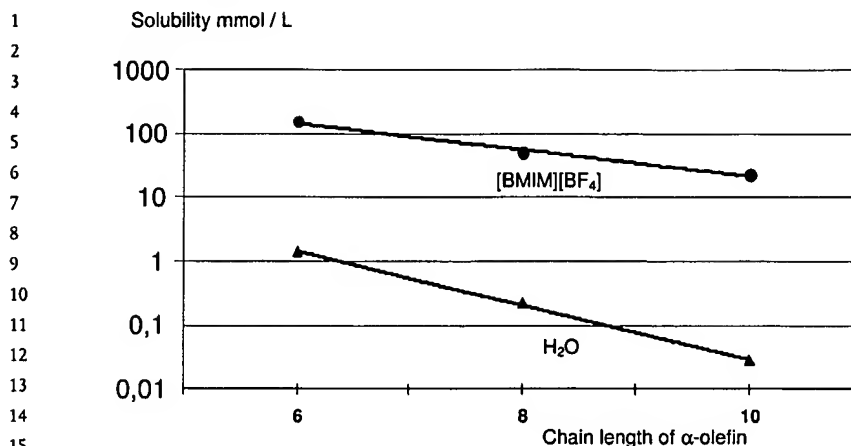


Fig. 5.4-2 Comparison of the solubility of  $\alpha$ -olefins with different numbers of carbon atoms in water and in  $[BMIM][BF_4]$ .

of ethanol, whereas the ionic liquid itself is only partially miscible with pure water or pure ethanol [13]. The mixing of different salts can also result in systems with modified properties (e.g. conductivity, melting point).

One of the key factors controlling the reaction rate in multiphasic processes (for reactions taking place in the bulk catalyst phase) is the reactant solubility in the catalyst phase. Thanks to their tunable solubility characteristics, the use of ionic liquids as catalyst solvents can be a solution to the extension of aqueous two-phase catalysis to organic substrates presenting a lack of solubility in water, and also to moisture sensitive reactants and catalysts. With the different examples presented below, we will report how ionic liquids can have advantageous effects on reaction rate and selectivity of homogeneous catalyzed reactions.

#### 5.4.4

##### Different Technical Solutions to Catalyst Separation through the Use of Ionic Liquids

In general, homogeneous catalysis suffers from complicated and expensive catalyst separation from the products. Homogeneous catalysts are very often unstable at the high temperatures necessary for the distillation of high boiling products. Multiphasic catalysis makes possible the separation of products under mild conditions. Different technologies to separate the products, and to recycle the catalytic system when using ionic liquids as one of these phases, have been proposed (Table 5.4-2).

The simplest case (Table 5.4-2, case (a)) is when the ionic liquid is able to dissolve the catalyst, and displays a partial solubility with the substrates and a poor solubility with the reaction products. Under these conditions, the product upper phase, also containing the unconverted reactants, is removed by simple phase decantation,

Table 5.4-2 Different technologies for multiphasic reactions making use of ionic liquids

Lower phase (during the reaction)	Upper phase (during the reaction)	Mode of separation catalyst phase/products	Ref.
Ionic liquid + catalyst	Organic liquid (Products + unreacted substrates)	a) Decantation (liquid-liquid)	[50]
Ionic liquid + catalyst + part of the products	Organic liquid (part of the products + unreacted substrates)	b) Filtration of the ionic liquid on cooling	[14, 15]
or	or	c) Product extraction with an organic co-solvent immiscible with the ionic liquid	[18]
Ionic liquid + catalyst + products	No upper phase	d) Distillation	[16]
		e) Separation after addition of a co-solvent miscible with the ionic liquid, immiscible with the products	
Ionic liquid + catalyst	Products + unreacted substrates + CO <sub>2</sub>	f) Extraction with ScCO <sub>2</sub>	[19]
Supported ionic liquid + catalyst	Organic liquid (products) or gas	g) Phase separation	[21]

and the ionic liquid containing the catalyst is recycled. This can be illustrated by transition-metal catalyzed olefin transformations to non-polar hydrocarbon products such as olefin oligomerization, hydrogenation, isomerization, metathesis and acidic olefin alkylation with isobutane. Transition-metal catalysts can also be immobilized in ionic liquids with melting points just above room temperature (Table 5.4-2, case (b)). The reaction occurs in a two-phase liquid–liquid system. By cooling the reaction mixture, the products can be separated by filtration from the “solid” catalyst medium, which can then be recycled. The advantages of this technique have been demonstrated for the hydrogenation of 1-hexene catalyzed by ruthenium-phosphine complexes in [BMIM][Cl]/ZnCl<sub>2</sub> [14] and for the hydroformylation of 1-hexene in the high melting phosphonium tosylate ionic liquids [15].

Because of the low vapor pressure of ionic liquids, product distillation without azeotrope formation can reasonably be anticipated if the products are not too high boiling. An example is given by the hydroformylation of methyl-3-pentenoate in [BMIM][PF<sub>6</sub>] with catalysis by a homogeneous Rh-phosphite system. In the absence of ionic liquid, deactivation of the catalyst is observed. Through the use of the [BMIM][PF<sub>6</sub>] salt, the catalyst is stabilized and can be successfully reused after distillation of the products [16]. Nevertheless, this separation technique remains demanding in energy, and the eventual accumulation of high-boiling by-products in the non-volatile ionic liquid phase can be a problem.

When the products are partially or totally miscible in the ionic phase, separation is much more complicated (Table 5.4-2, cases (c)–(e)). One advantageous option can be to perform the reaction in one single phase, thus avoiding diffusional limitation, and to separate the products in a further step by extraction. Such technology has already been demonstrated for aqueous biphasic systems. This is the case for the palladium-catalyzed telomerization of butadiene with water, developed by Kuraray, which uses a sulfolane/water mixture as the solvent [17]. The products are soluble in water, which is also the nucleophile. The high-boiling by-products are extracted with a solvent (such as hexane) that is immiscible in the polar phase. This method has the advantage that (i) the catalyst and the products can be separated without heating them, so that thermal deactivation is avoided, and (ii) the extraction is achieved for all the compounds, so that the accumulation of catalyst poisons and high boiling by-products is minimal. This technology can be applied when ionic liquids are used as the catalyst polar phase (Fig. 5.4-3).

A co-solvent that is poorly miscible with ionic liquids but highly miscible with the products can be added in the separation section (after the reaction) to facilitate the product separation. The Pd-mediated Heck coupling of aryl halides or benzoic anhydride with alkenes, for example, can be performed in [BMIM][PF<sub>6</sub>], the products being extracted with cyclohexane. In this case, water can also be used as an extraction solvent, to remove the salt by-products formed in the reaction [18]. From a practical point of view, the addition of a co-solvent can result in cross-contamination, and it has to be separated from the products in a supplementary step (distillation). More interestingly, unreacted organic reactants themselves (if they have a non-polar character) can be recycled to the separation step and can be used as the extractant co-solvent [19].

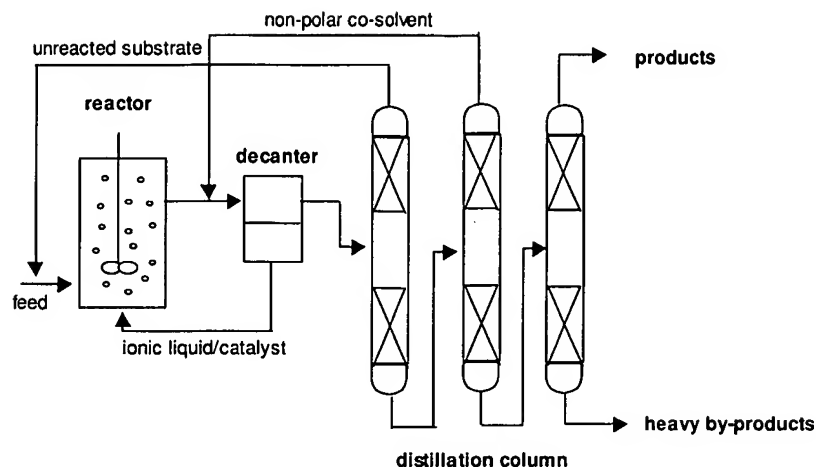


Fig. 5.4-3 Example of extraction method for product separation from ionic liquid/catalyst reaction mixture.

When water-miscible ionic liquids are used as solvents, and when the products are partly or totally soluble in these ionic liquids, the addition of polar solvents, such as water, in a separation step after the reaction can make the ionic liquid more hydrophilic and facilitate the separation of the products from the ionic liquid/water mixture (Table 5.4-2, case (e)). This concept has been developed by Union Carbide for the higher alkene hydroformylation catalyzed by Rh-sulfonated phosphine ligand in an *N*-methylpyrrolidone (NMP)/water system. Thanks to the presence of NMP, the reaction is performed in one homogeneous phase. After the reaction, water is added in a mixer followed by efficient phase separation in a settler. One advantage of this process is its flexibility and good performance with respect to the olefin carbon number.

The combination of ionic liquids with supercritical carbon dioxide is an attractive approach as both these solvents present complementary properties (volatility, polarity scale, etc.). Compressed CO<sub>2</sub> dissolves quite well in ionic liquids, but ionic liquids do not dissolve in CO<sub>2</sub>. It decreases the viscosity of ionic liquids, thus facilitating mass transfer during catalysis. The separation of the products can be effective in a solvent-free form and the CO<sub>2</sub> can be recycled by recompressing it back into the reactor. Continuous flow catalytic systems based on the combination of these two solvents have been reported [19]. This concept is developed in more detail in Section 5.7.

Membrane techniques have already been combined with two-phase liquid catalysis. The main function of this method is to perform fine separation of undesirable constituents from the catalytic system after phase decantation has already performed the coarse separation of the catalyst from the products. This technique can be

## 472 | 5 Organic Synthesis

1 applied to ionic liquid systems as a promising approach for the selective removal of  
2 volatile solutes from ionic liquids [20].

3 Ionic liquids have been demonstrated to be effective membrane materials for gas  
4 separation when supported within a porous polymer support. However, supported  
5 ionic liquid membranes offer another versatile approach by which to perform two-  
6 phase catalysis. This technology combines some of the advantages of an ionic  
7 liquid as catalyst solvent with the ruggedness of the ionic liquid-polymer gels.  
8 Transition-metal complexes based on palladium or rhodium have been incorporated  
9 into a gas-permeable polymer gel composed of [BMIM][PF<sub>6</sub>] and poly(vinylidene  
10 fluoride)-hexafluoropropylene copolymer and then were used to investigate the  
11 hydrogenation of propene [21].

## 13 5.4.5

## 14 Immobilization of Catalysts in Ionic Liquids

15  
16 Two main methodologies have been developed for the use of ionic liquids in catalytic  
17 or organic reactions. In the first, the ionic liquid is both the catalyst and the reaction  
18 solvent. An example is acid-catalyzed reactions in which Lewis acidic ionic liquids  
19 such as acidic chloroaluminates are both active catalytic species and solvents of  
20 carbenium ions. In this case, dissolution of the inorganic Lewis acid (e.g. AlCl<sub>3</sub>)  
21 in the organic phase is not observed. In the second approach, discussed in Section  
22 5.3, the ionic liquid acts as a "liquid support" of homogeneous catalysts. In this  
23 technology, the catalyst (in general a transition-metal complex) is immobilized in  
24 the ionic phase and the products form the upper phase, as described in Section  
25 5.4.4. To achieve the development of such an approach in a continuous process,  
26 the key point is to immobilize and stabilize the catalyst in the ionic liquid in the  
27 presence of an organic second phase with minimum loss of metal. Two approaches  
28 have been investigated:

- 29
- 30
- 31 1 The active species is known to be ionic in organic conventional solvents.
- 32 2 The active species is characterized as a non-charged complex.
- 33

34 In the first case, one may expect that the catalyst should remain ionic and be  
35 retained without modification in the ionic liquid. Different successful examples  
36 have been reported, such as hydrogenation reactions catalyzed by the cationic  
37 [HRh(PPh<sub>3</sub>)<sub>2</sub>(diene)][PF<sub>6</sub>] complexes [22] and aromatic hydrogenation catalyzed  
38 by the [H<sub>4</sub>Ru<sub>4</sub>(C<sub>6</sub>H<sub>6</sub>)<sub>4</sub>][BF<sub>4</sub>]<sub>2</sub> cluster [23]. In the presence of hydrogen, this later  
39 complex probably forms the [H<sub>6</sub>Ru<sub>4</sub>(C<sub>6</sub>H<sub>6</sub>)<sub>4</sub>][BF<sub>4</sub>] complex, which acts as the  
40 effective arene hydrogenation catalyst. Another example is olefin dimerization cat-  
41 alyzed by the cationic [HNi(olefin)][A] (A is a chloroaluminate anion) complexes.  
42 These species can be formed by *in situ* alkylation of a nickel (II) salt with an acidic  
43 alkylchloroaluminate ionic liquid acting both as the solvent and as the co-catalyst  
44 [24]. The cationic [(methallyl)Ni(Ph<sub>2</sub>PCH<sub>2</sub>PPh<sub>2</sub>(O))][SbF<sub>6</sub>] complex proved to be stable  
45 and active for ethene oligomerization in [PF<sub>6</sub>]<sup>-</sup>-based ionic liquids without the

1 addition of Lewis acid. The high electrophilicity of the Ni center, which is respon-  
2 sible for the activity of the catalyst, is probably not altered by the ionic solvent [25].  
3 In the Suzuki reaction, the active species in [BMIM][BF<sub>4</sub>] is believed to be the trico-  
4 ordinated [Pd(PPh<sub>3</sub>)<sub>2</sub>(Ar)]X complex that forms after oxidative addition of the aryl  
5 halide to [Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>4</sub>] [26]. Because of their low nucleophilicity, ionic liquids do not  
6 compete with the unsaturated organic substrate for coordination to the electrophilic  
7 active metal center. The different recycle experiments demonstrate the stability of  
8 these organometallic complexes in ionic liquids.

9 Not only cationic, but also anionic, species can be retained without addition of  
10 specially designed ligands. The anionic active [HPt(SnCl<sub>3</sub>)<sub>4</sub>]<sup>3-</sup> complex has been  
11 isolated from the [NEt<sub>4</sub>][SnCl<sub>3</sub>] solvent after hydrogenation of ethylene [27]. The  
12 PtCl<sub>2</sub> precursor used in this reaction is stabilized by the ionic salt (liquid at the  
13 reaction temperature) since no metal deposition occurs at 160 °C and 100 bar. The  
14 catalytic solution can be used repeatedly without apparent loss of catalytic activity.

15 In the second case, in which the active catalytic species is assumed to be un-  
16 charged, leaching of the transition metal in the organic phase can be limited by  
17 the use of functionalized ligands. As the triumph of aqueous biphasic catalysis  
18 follows the laborious work involved in the development of water-soluble ligands,  
19 recent investigations have focused on the synthesis of new ligands with tailor-made  
20 structures for highly active and selective two-phase catalysts and for good solubility  
21 in the ionic liquid phase [28]. These ligands are mainly phosphorus ligands with  
22 appropriate modifications (Scheme 5.4-1).

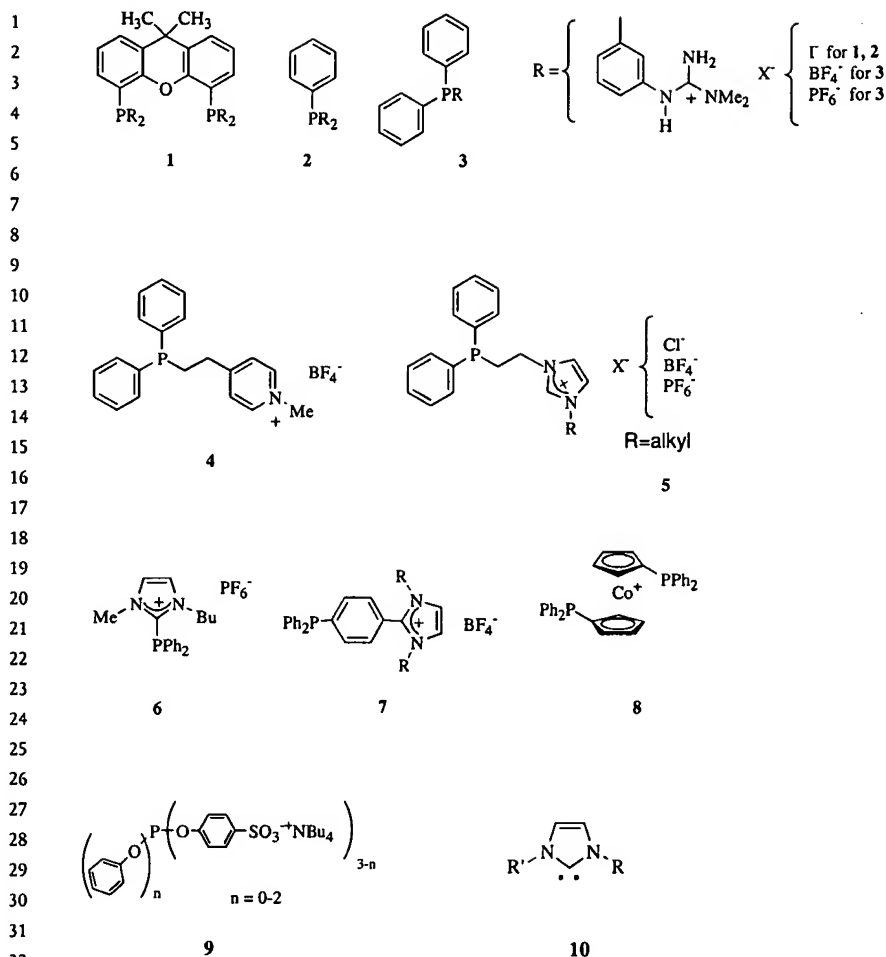
23 Polar groups such as the cationic phenylguanidinium 1–3 [29, 30], imidazolium  
24 and pyridinium groups 4 and 5 [31], and the 2-imidazolyl groups 6 and 7 [32]  
25 have been reported. A cobaltocinium salt bearing phosphine donors 8 [33] has also  
26 been described. Phosphites are well known ligands in homogeneous Rh-catalyzed  
27 hydroformylation affording enhanced reaction rates and regioselectivities. Since  
28 they are unstable towards hydrolysis, examples of their use in aqueous biphasic  
29 catalysis are rare. Ionic liquids offer suitable alternative solvents compatible with  
30 phosphites 9 [29].

31 To date, these functionalized ligands have been investigated on the laboratory  
32 scale, in batch operation to immobilize the rhodium catalyst in hydroformylation.  
33 Good rhodium retention results were obtained after several recycles. However,  
34 optimized ligand/metal ratio and leaching and decomposition rates, which can  
35 result in the formation of inactive catalyst, are not known for these ligands and  
36 testing in continuous mode is required. As a reference, in the Ruhrchemie-Rhône  
37 Poulenc process, the losses of rhodium are <10<sup>-9</sup> g Rh per kg n-butyraldehyde.

38 Certain amines, when linked to TPPTS, form ionic solvents liquid at quite low  
39 temperature. Bahrman [34] used these ionic liquids as both ligands and solvents for  
40 the Rh catalyst for the hydroformylation of alkenes. In this otherwise interesting  
41 approach, however, the ligand/rhodium ratio, which influences the selectivity of  
42 the reaction, is difficult to control.

43 As well as phosphorus ligands, heterocyclic carbene ligands 10 have proven to  
44 be interesting donor ligands for stabilization of transition metal complexes (espe-  
45 cially palladium) in ionic liquids. The imidazolium cation is usually presumed to

## 474 | 5 Organic Synthesis

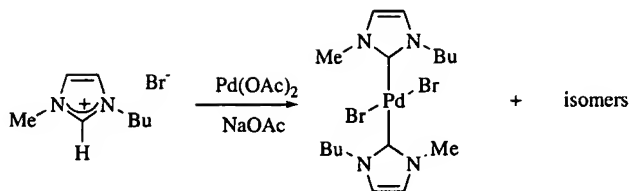


Scheme 5.4-1 Ligands 1–10.

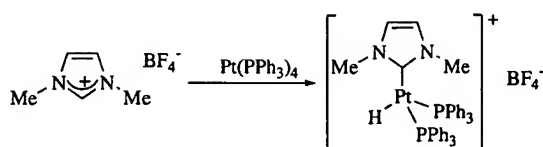
be a simple inert component of the solvent system. However, the proton on the carbon atom at position 2 in the imidazolium is acidic and this carbon atom can be deprotonated by, for example, basic ligands of the metal complex, to form carbenes (Scheme 5.4-2).

The ease of formation of the carbene depends on the nucleophilicity of the anion associated with the imidazolium. For example when  $\text{Pd}(\text{OAc})_2$  is heated in the presence of  $[\text{BMIM}][\text{Br}]$ , the formation of a mixture of Pd imidazolylidene complexes occurs. Palladium complexes have been shown to be active and stable catalysts for Heck and other C–C coupling reactions [35]. The highest activity and stability of palladium is observed in the ionic liquid  $[\text{BMIM}][\text{Br}]$ . Carbene complexes





**Scheme 5.4-2** Formation of carbene complexes by dialkylimidazolium salt deprotonation.



**Scheme 5.4-3** Formation of carbene complexes by oxidative addition to Pt(0).

can be formed not only by deprotonation of the imidazolium cation but also by direct oxidative addition to metal(0) (Scheme 5.4-3). These heterocyclic carbene ligands can be functionalized with polar groups in order to increase their affinity for ionic liquids. While their donor properties can be compared to those of donor phosphines, they have the advantage over phosphines of being stable toward oxidation.

#### 5.4.6

#### The Scale-up of Ionic Liquid Technology from Laboratory to Continuous Pilot Plant Operation

The increasing number of applications that make use of ionic liquids as solvents or catalysts for organic and catalytic reactions emphasizes their key advantages over organic solvents and their complementarity with respect to water or other "green" solvents. For scaling up to large-scale production, however, kinetic models are very often required and have to be developed for an optimum reactor design. In this type of multiphase (biphasic) catalysis, one important parameter is the location of the reaction: does the reaction take place in the bulk of the liquid, at the interface or simultaneously at both sites? For a reaction in the bulk of the liquid (e.g. in the ionic liquid), the liquid (and/or gaseous) reactants would first have to dissolve in the catalyst solution phase before the start of the chemical reaction. The reaction rate would therefore be determined by the concentration of the reactants in the catalyst phase. It is important to be able to identify mass transfer limitations that occur when the reaction rate is higher than the mass transfer velocity. In some cases the existence of mass transfer limitations can be used advantageously to control the exothermicity of reactions. For example, a reduction in stirring can be a means to decrease the reaction rate without having to destroy the catalyst. In single phase homogeneous

1 reactions, catalyst poisons (such as CO or CO<sub>2</sub>) are sometimes deliberately injected  
2 in the reactor to stop the reaction.

3 In the aqueous biphasic hydroformylation reaction, the site of the reaction has  
4 often been discussed (and contested) and is dependent on reaction conditions  
5 (temperature, partial pressure of gas, stirring, use of additives) and reaction partners  
6 (type of alkene) [36, 37]. It has been suggested that the positive effects of co-solvents  
7 indicate that the bulk of the aqueous liquid phase is the reaction site. By contrast,  
8 the addition of surfactants or other surface- or micelle-active compounds accelerates  
9 the reaction, which apparently indicates that the reaction occurs at the interfacial  
10 layer.

11 Therefore, important parameters such as phase transfer phenomena (i.e. solubil-  
12 ity of the reactants in the ionic liquid phase), volume ratio of the different phases,  
13 efficiency of mixing so as to provide maximum liquid-liquid interfacial area, are key  
14 factors in determining and controlling reaction rates and kinetics. Kinetic models  
15 have been developed for aqueous biphasic systems and are continuously refined to  
16 improve agreement with experimental results. These models might be transferable  
17 to biphasic catalysis with ionic liquids, but more data concerning the solubility of  
18 liquids (and gas) in these new solvents and the existence of phase equilibria in the  
19 presence of organic upper phases have still to be accumulated (see Sections 3.3 and  
20 3.4).

21 The influence of the concentration of hydrogen in [BMIM][PF<sub>6</sub>] and [BMIM][BF<sub>4</sub>]  
22 on the asymmetric hydrogenation of  $\alpha$ -acetamidocinnamic acid catalyzed by  
23 rhodium complexes bearing a chiral ligand has been investigated. Hydrogen was  
24 found to be four times more soluble in the [BF<sub>4</sub>]<sup>-</sup>-based salt than in the [PF<sub>6</sub>]<sup>-</sup>-based  
25 one, under the same pressure. This difference in molecular hydrogen concentration  
26 in the ionic phase (rather than pressure in the gas phase) has been correlated with  
27 the remarkable effect on the conversion and enantioselectivity of the reaction [38].

28 In the rhodium-catalyzed hydroformylation of 1-hexene, it has been demonstrated  
29 that there is a correlation between the solubility of 1-hexene in ionic liquids and  
30 reaction rates (Fig. 5.4-4) [29].

31 However, information concerning the characteristics of these systems under the  
32 conditions of a continuous process is still very limited. From a practical point of  
33 view, the concept of ionic liquid multiphasic catalysis can be applicable only if the  
34 resultant catalytic lifetimes and the elution losses of catalytic components into the  
35 organic or extractant layer containing products are within commercially acceptable  
36 ranges. To illustrate these points, two examples of applications run on continuous  
37 pilot operation will be described: (i) biphasic dimerization of olefins catalyzed by  
38 nickel complexes in chloroaluminates, and (ii) the biphasic alkylation of aromatic  
39 hydrocarbons with olefins and light olefin alkylation with isobutane, catalyzed by  
40 acidic chloroaluminates.

#### 41 5.4.6.1 Dimerization of Alkenes Catalyzed by Ni complexes

42 The Institut Français du Pétrole has developed and commercialized a process,  
43 named Dimersol X, based on a homogeneous catalyst, which selectively pro-  
44 duces dimers from butenes. The low-branching octenes produced are good starting  
45

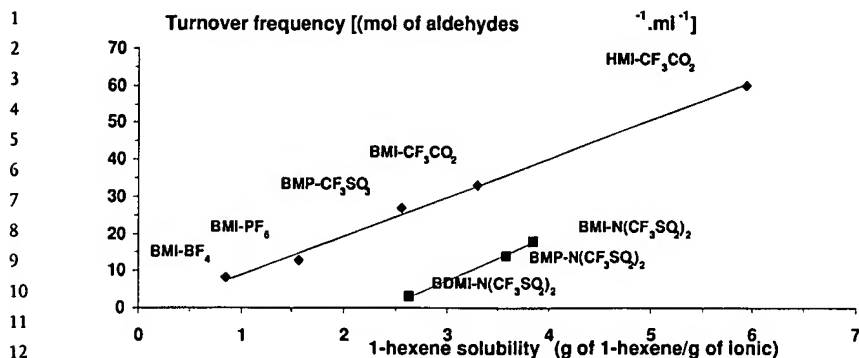


Fig. 5.4-4 Turnover frequency of Rh-catalyzed hydroformylation as a function of 1-hexene solubility in the ionic liquids. Reaction conditions: Rh(CO)<sub>2</sub>(acac) 0.075 mmol, 1-hexene/Rh = 800, TPPTS/Rh = 4, heptane as internal standard, CO/H<sub>2</sub> = 1 (molar ratio), *P* = 2 MPa, *T* = 80 °C, TOF determined at 25% conversion of 1-hexene. [BMP] = *N,N*-butylmethylpyrrolidinium; [BMMIM] = 1-butyl-2,3-dimethylimidazolium.

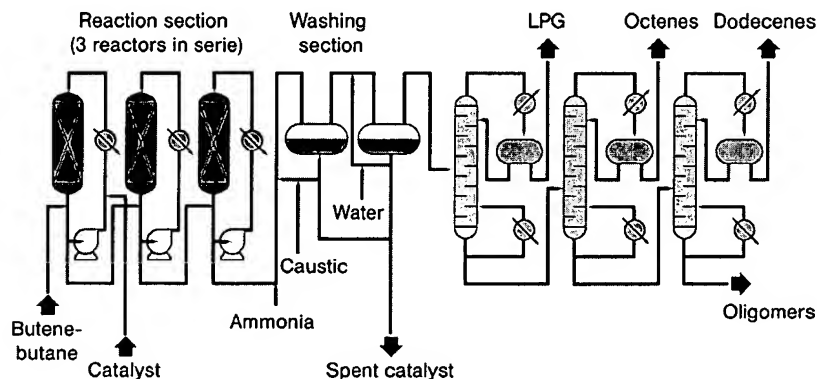


Fig. 5.4-5 Dimersol process.

materials for isononanol production. This process is catalyzed by a system based on a nickel(II) salt, soluble in a paraffinic hydrocarbon, activated with an alkylaluminum chloride co-catalyst directly inside the dimerization reactor. The reaction is second order in monomer concentration and first order in catalyst concentration. The butene conversion level is highly dependent on its initial concentration in the feed. For 70 wt.% butene concentration in the feed, commercial Dimersol X technology can achieve 80% conversion of butenes with 85% octene selectivity. A process flow diagram is shown in Fig. 5.4-5.

## 478 | 5 Organic Synthesis

Table 5.4-3 Solubilities of 1-butene and n-butane in the acidic mixture composed of 1-butyl-3-methyl imidazolium chloride: aluminum chloride: ethylaluminum dichloride (1:1.22:0.06 molar ratio) as a function of temperature and under atmospheric pressure

Temperature (°C)	Solubility of 1-butene (wt.%) <sup>[a]</sup>	Solubility of butane (wt.%)
10	4.5	2
20	2	1

<sup>a</sup>Isomerization of 1-butene into 2-butene is observed.

The reaction takes place at low temperature (40–60 °C) in a series of well-mixed reactors (two or more, up to four). The pressure is chosen to maintain all reactants and products in the liquid phase (no gas phase). Mixing and heat removal are ensured by an external circulation loop over a heat exchanger system. The two components of the catalytic system are injected separately into the circulation loop with precise flow control. The residence time in the reactor can be between 5 and 10 h. At the outlet of the reaction section, the catalyst present in the effluent is chemically neutralized and the products are washed with caustic soda and water to remove the deactivated catalyst. The catalyst components are not recycled. The product effluent is finally distilled to remove unreacted olefins and inert hydrocarbons, which can be used as such (LPG), or sent back to the cracker. The octenes are finally separated from the heavier oligomers by another distillation column. The Dimersol catalytic system is sensitive to impurities, such as polyunsaturated hydrocarbons or polar compounds that can strongly coordinate to the nickel metal center or react with the alkylaluminum chloride co-catalyst. A light pre-treatment is usually sufficient to remove such impurities.

Despite all the advantages of this process, one main limitation is the continuous catalyst carry-over by the products, with the need to deactivate it and dispose of wastes. One way to optimize catalyst consumption and waste disposal is to operate the reaction in a biphasic system. The first difficulty was to choose a “good” solvent. *N,N'*-Dialkylimidazolium chloroaluminate ionic liquids proved to be the best candidates. They are liquid at the reaction temperature, butenes are reasonably soluble in them (Table 5.4-3), and they are poorly miscible with the products (Table 5.4-2, case (a)). The chloroaluminate efficiently dissolves and stabilizes the nickel catalyst in the ionic medium without the addition of special ligand. The ionic liquid plays the role of both catalyst solvent and co-catalyst. Its Lewis acidity can be adjusted to get the best performance. The catalytically active nickel complex is generated directly in the ionic liquid by reaction of a commercialized nickel(II) salt, as used in the Dimersol process, with an alkylaluminum chloride derivative.

The biphasic system has been evaluated in terms of activity, selectivity, recyclability and lifetime of the ionic liquid, in a continuous flow pilot operation. A representative industrial feed (Raffinate II), composed of 70 wt.% butenes (27% of which is 1-butene) and 1.5 wt.% isobutene (the remainder being n-butane and isobutane) enters continuously into the well mixed reactor containing the ionic

liquid and the nickel catalyst. Injection of fresh catalyst components can be made to compensate for the detrimental effects of random impurities present in the feed and for a slight catalyst carryover by the organic phase. The reactor is operated full of liquid. The effluent (a mixture of the two liquid phases) leaves the reactor through an overflow and is transferred to a phase separator. The separation of the ionic liquid (density around  $1200 \text{ g L}^{-1}$ ) and the oligomers occurs rapidly and completely (favored by the difference in densities). The ionic liquid and the catalyst are recycled to the reactor. A continuous run has been carried out over a period of 5500 h with an industrial Raffinate-2 feed. Throughout the whole duration of the run, the conversion of butenes was more than 70 wt.% and the octene selectivity around 95 wt.%. This is about 10 wt.% more than the selectivity already obtained with the monophasic homogeneous Dimersol X. With the biphasic system, octene selectivity remained higher than 90%, even for 80 wt.% butene conversion. This higher selectivity is a direct consequence of the low solubility of octenes in the ionic liquid. In the monophasic Dimersol system, at high monomer conversion, the high concentration of dimers induces increasing production of trimers and tetramers through a consecutive mechanism. In the biphasic system, the low solubility of octenes in the ionic phase containing the catalyst reduces consecutive reactions and enhances octene selectivity. After the 5500 h of running, the test was deliberately stopped. The addition of fresh ionic liquid was not required during the test, which demonstrates the stability of the ionic liquid under the reaction conditions. Relative to the homogeneous Dimersol process, the nickel consumption was decreased by a factor of 10.

Despite the utmost importance of physical limitations such as solubility and mixing efficiency of the two phases, an apparent first-order reaction rate relative to the olefin monomer was determined experimentally. It has also been observed that an increase in the nickel concentration in the ionic phase results in an increase in the olefin conversion.

In the homogeneous Dimersol process, the olefin conversion is highly dependent on the initial concentration of monomer in the feed, which limits the applicability of the process. The biphasic system is able to overcome this limitation and promotes the dimerization of feeds poorly concentrated in olefinic monomer.

The ratio of the ionic liquid to the organic phase present in the reactor also plays an important role. A too high level of ionic liquid results in much longer decantation time and causes lower dimer selectivity.

Based on these results a new biphasic process named Difasol has been developed (Fig. 5.4-6). Because of the solubility of the catalyst in the ionic phase and the poor miscibility of the products, the Difasol unit is essentially reduced to a continuous stirred tank reactor followed by a phase separator. As the mixing of the two phases plays an important role in determining the reaction rate, a mechanically stirred type reactor rather than a loop reactor was chosen. To combine efficient decantation and a reasonable size for the settler in the process design, it has been proposed that the separation of the two phases be performed in two distinct setting zones arranged in parallel [39]. The first settler has a moderate residence time and separates the ionic phase which is returned to the reactor while the organic phase is circulated, via a

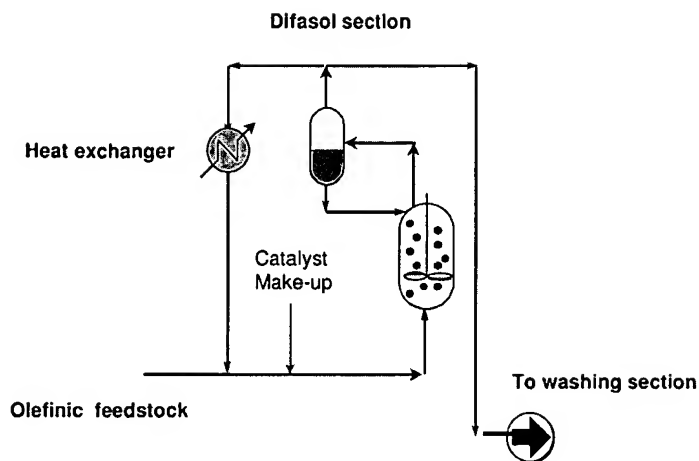


Fig. 5.4-6 Difasol reaction section.

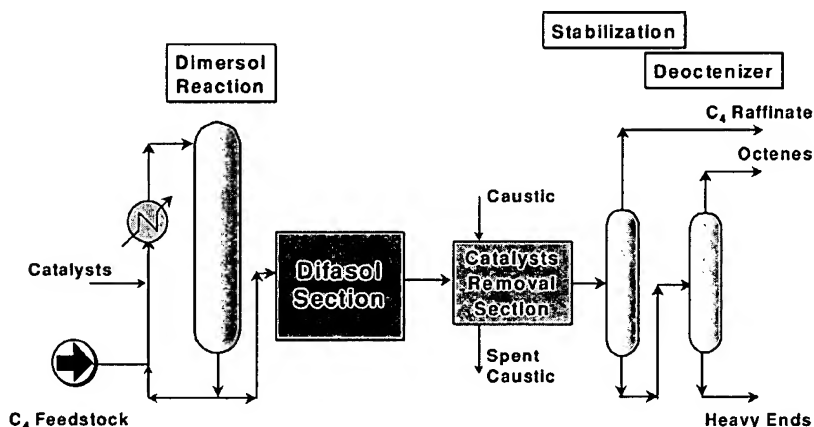


Fig. 5.4-7 Process scheme integrating Dimersol and Difasol.

pump-around through a heat exchanger. The other settler has a longer residence time and sends product phase to the neutralization section. The Difasol reaction section and settling sections can ideally be integrated as a finishing reaction section after a first homogeneous Dimersol reactor (Fig. 5.4-7). The high Difasol efficiency on diluted feed, such as unreacted butenes exiting the Dimersol reactor, allows such a combination. This first homogeneous step offers the possibility to purify the feed of trace impurities very efficiently. Another interesting approach to remove the impurities from the feed consists of circulating the feed to be treated and the ionic liquid already used in the dimerization section, as a counter-current [40].

Table 5.4-4 Comparison of performance between homogeneous Dimersol process and [Dimersol + Difasol] arrangement with a feed containing 79 wt.% butenes

	Dimersol	Dimersol + Difasol
Octenes yield	0.68	0.75
Relative nickel consumption	100	70

Table 5.4-5 Unit performances: Butenes conversion and oligomer selectivity with a feed containing 79 wt.% butenes

	Dimersol unit	[Dimersol + Difasol] arrangement		
		Dimersol reactor	Difasol reactor	Global arrangement
Conversion (%)	80	50	75	81
Selectivity (%)	85	93	91	92
Relative chemical consumption (including IL) per ton octenes	Base: 100			82

Table 5.4-6 CAPEX and OPEX comparison for the two arrangements Dimersol and [Dimersol + Difasol]

Unit configuration	Dimersol	[Dimersol + Difasol]
Total investment (a)	Base: 100	95
Octenes yield (%) (b)	68	75
relative CAPEX per ton of octenes ((a)/(b))	1.5	1.3
Total utilities and chemicals (c)	Base: 100	92
relative OPEX per ton of octenes ((c)/(b))	1.5	1.2

Basis: C4 Feed 160 000 t a<sup>-1</sup> C4 cut. Feed 79 wt.% butenes.

The Dimersol-Difasol arrangement ensures more efficient overall catalyst utilization and an increase in the yield of octenes by about 10 wt.% (Table 5.4-4). Table 5.4-5 shows a simplified mass balance comparison for the Dimersol process and the [Dimersol + Difasol] combination. In the [Dimersol + Difasol] arrangement, the catalyst consumption in the Dimersol reactor is reduced to induce a low intermediate conversion. The Difasol reactor converts the remaining butenes. Both butene conversion and octene selectivity are clearly improved using the [Dimersol + Difasol] arrangement. This arrangement features very interesting CAPEX and OPEX savings per ton of octenes produced (Table 5.4-6).

The ionic liquid-based Difasol technology improves further the performance of the classical Dimersol for lightly branched octenes production. Since the catalyst is concentrated and operates in the ionic phase and also probably at the phase

boundary, the reaction volume is much lower in the biphasic technology compared to the conventional single-phase Dimersol process, in which the catalyst concentration in the reactor is very low [41].

A similar dimerization catalytic system has been investigated [42] in a continuous flow loop reactor in order to study the stability of the ionic liquid solution. The catalyst used is the organometallic nickel(II) complex (Hcod)Ni(hfacac) (Hcod=cyclooct-4-ene-1-yl and hfacac=1,1,1,5,5,5-hexafluoro-2,4-pentanedionato-O,O') and the ionic liquid is an acidic chloroaluminate based on the acidic mixture of 1-butyl-4-methylpyridinium chloride and aluminum chloride. No alkylaluminum is added, but an organic Lewis base is added to buffer the acidity of the medium. The ionic catalyst solution is introduced in the reactor loop at the beginning of the reaction and the loop is filled with the reactants (total volume 160 mL). The feed enters continuously in the loop and the products are continuously separated in a settler. The overall activity is 18.000 (TON). The selectivity to dimers is in the 98% range and the selectivity to linear octenes is 52%.

#### 5.4.6.2 Alkylation Reactions

BP Chemicals studied the use of chloroaluminates as acidic catalysts and solvents for aromatic alkylation [43]. At present, the  $\text{AlCl}_3$  existing technology (based on "red oil" catalyst) is still used industrially, but continues to suffer from poor catalyst separation and recycle [44]. The aim of the work was to evaluate the  $\text{AlCl}_3$ -based ionic liquids, with the emphasis placed on the development of a clean and recyclable system for the production of ethylbenzene (benzene/ethene alkylation) and synthetic lubricants (alkylation of benzene with 1-decene). The production of linear alkyl benzene (LAB) has also been developed by Akzo [45]. The ethylbenzene experiments were run by BP in a pilot loop reactor similar to that described for the dimerization (Fig. 5.4-8).

Ionic liquids operate in true biphasic mode. While the recovery and recyclability of the ionic liquid was found to be more efficient than with the conventional  $\text{AlCl}_3$  catalyst (red oil), the selectivity to the monoalkylated aromatic hydrocarbon was lower. In this gas-liquid-liquid reaction, the solubility of the reactants in the ionic phase (e.g. the ratio benzene/ethene in the ionic phase) and the mixing of the phases were probably critical. This is an example where the engineering aspects are of the utmost importance.

The use of acidic chloroaluminates as alternative liquid acid catalysts for the alkylation of light olefins with isobutane, for the production of high octane number gasoline blending components, is also a challenge. This reaction has been performed in a continuous flow pilot plant operation at IFP [46] in a reactor vessel similar to that used for dimerization. The feed, a mixture of olefin and isobutane, is pumped continuously into the well-stirred reactor containing the ionic liquid catalyst. In the case of ethene, which is less reactive than butene, [pyridinium]Cl/ $\text{AlCl}_3$  (1:2 molar ratio) ionic liquid proved to be the best candidate (Table 5.4-7).

The reaction can be run at room temperature and provides good quality alkylate (dimethylbutanes are the major products) over a period of 300 h. When butenes are used instead of ethene, lower temperature and a fine-tuning of the acidity of the



Table 5.4.7 Alkylation of ethylene and 2-butene with isobutane. Semi-continuous pilot-plant results

Operating conditions/nature of the olefin		Ethene	2-Butene
Nature of ionic liquid			
Olefin content in the feed (wt.%)		[Pyridinium, HCl]/AlCl <sub>3</sub> (1:2 molar ratio)	[BMIM][Cl]/AlCl <sub>3</sub>
VVH <sup>a</sup> (h <sup>-1</sup> )		14–20	12–14
Temperature (°C)		0.2	0.35–0.45
Test duration (h)		25	5
Olefin conversion (wt.%)		354	520
Production (g products/g ionic liquid)		60–90	>98
Product distribution (wt.%)		121	172
		i-C <sub>6</sub> <sup>b</sup>	Light ends <sup>e</sup> :
		i-C <sub>8</sub> <sup>c</sup>	i-C <sub>8</sub> <sup>c</sup>
		C <sub>8</sub> <sup>+</sup> <sup>d</sup>	C <sub>8</sub> <sup>+</sup> <sup>d</sup>
		90–94	90–95
MON <sup>f</sup>		98–101	95–98
RON <sup>f</sup>			

<sup>a</sup>volume of olefin/(volume of ionic liquid hour).<sup>b</sup>i-C<sub>6</sub> = 2,2- and 2,3-dimethylbutanes.<sup>c</sup>i-C<sub>8</sub> = isooctanes.<sup>d</sup>C<sub>8</sub><sup>+</sup> = hydrocarbon products having more than eight carbon atoms.<sup>e</sup>Light ends = hydrocarbon products with fewer than eight carbon atoms.<sup>f</sup>RON = research octane number, MON = motor octane number.

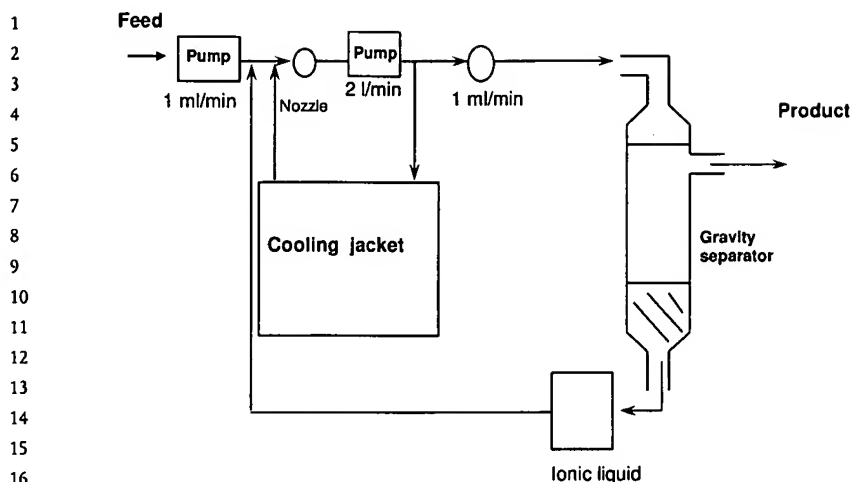


Fig. 5.4-8 Loop reactor as used in aromatic hydrocarbon alkylation experiments.

ionic liquid are required to avoid cracking reactions and heavy by-product formation. Continuous butene alkylation has been performed for more than 500 h with no loss of activity and stable selectivity. A high level of mixing is essential for a high selectivity and thus for a good quality alkylate. These applications are promising, but efforts are still needed to compete with the existing effective processes based on hydrofluoric and sulfuric acids.

#### 5.4.6.3 Industrial Use of Ionic Liquids

What can drive the switch from homogeneous existing processes to novel biphasic ionic liquid technologies? One major point is probably a higher cost-effectiveness. This can result from improved reaction rate and selectivity, associated with more efficient catalyst recovery and better environmental compatibility. The cost of ionic liquids can, of course, be a limiting factor to their development. However, this cost has to be weighed against that of current chemicals or catalysts. If the ionic liquid can be recycled and if its lifetime proves to be long enough, then its initial price is probably not the critical point. In Difasol technology, for example, ionic liquid cost, expressed with respect to the octenes produced, is lower than that of catalyst components.

The manufacture of ionic liquids on an industrial scale is also to be considered. [BMIM]Cl is already a commercial ionic liquid that has been produced by BASF on a ton scale [47]. Chloroaluminate laboratory preparations proved to be easily extrapolated to large scale. These chloroaluminate salts are corrosive liquids in the presence of protons. When exposed to moisture, they produce hydrochloric acid, similarly to aluminum chloride. However, this can be avoided by the addition of some proton scavenger such as alkylaluminum derivatives. In Difasol technology,

1 for example, carbon-steel reactors can be used with no corrosion problem. The  
2 purity of ionic liquids is a key parameter especially when they are used as solvents  
3 for transition-metal complexes (see Section 5.3). The presence of impurities arising  
4 from their mode of preparation can change their physical and chemical properties.  
5 Even trace amounts of impurities (e.g. Lewis bases, water, chloride anion) can  
6 poison the active catalyst, due to its generally low concentration in the solvent. The  
7 control of ionic liquid quality is thus of the utmost importance.

8 As relatively new compounds, only limited research has been carried out to evalu-  
9 ate the biological effects of ionic liquids (see Section 2.2 and Chapter 10). The topical  
10 effect of [EMIM][Cl]/AlCl<sub>3</sub> melts and its organic compound [EMIM][Cl], on the in-  
11 tegument of laboratory rat has been investigated. The study reports that [EMIM][Cl]  
12 is not in itself responsible for tissue damage, however, the chloroaluminate salt  
13 can induce tissue irritation, inflammation and necrosis due to the presence of alu-  
14 minum chloride. However, treatments for aluminum chloride and hydrochloric  
15 acid are well-documented. Fortunately, a lot of different studies on the toxicity and  
16 ecotoxicity of ionic liquids are now under way [48]. Few data [49] relating to the  
17 disposal of used ionic liquids are available. In Difasol technology, the used ionic  
18 liquid is taken out of the production system and the reactor is refilled with fresh  
19 catalyst solution.

#### 22 5.4.7

#### 23 Concluding Remarks and Outlook

24  
25 Compared to classical processes involving thermal separation, biphasic techniques  
26 offer simplified process schemes and no thermal stress for the organometallic  
27 catalyst. The concept requires that the catalyst and the product phases separate  
28 rapidly, to achieve a practical approach to the recovery and recycling of the catalyst.  
29 Owing to their tuneable solubility characteristics, ionic liquids prove to be good  
30 candidates for multiphasic techniques. They extend the applications of aqueous-  
31 biphasic systems to a broader range of organic hydrophobic substrates and water-  
32 sensitive catalysts (see Section 5.3 and Ref. [50]).

33 To be applied industrially, performance must be superior to that of the exist-  
34 ing catalytic systems (activity, regioselectivity and recyclability). The use of ionic  
35 liquid biphasic technology for nickel-catalyzed olefin dimerization proved to be  
36 successful and this system has been developed and is now proposed for commer-  
37 cialization. However, much effort remains if the concept is to be extended to non-  
38 chloroaluminate ionic liquids. In particular, the true potential of ionic liquids (and  
39 mixtures containing ionic liquids) could be achievable if an even more substantial  
40 body of thermophysical and thermodynamic properties were amassed in order that  
41 the best medium for a given reaction could be chosen. As far as industrial applica-  
42 tions are concerned, the easy scale-up of two-phase catalysis can be illustrated by  
43 the first oxo commercial unit with an initial capacity of 100 000 tons extrapolated by  
44 a factor of 1:24 000 (batch-wise laboratory development to production reactor) after  
45 a development period of 2 years [4].

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## 5.5 Task-specific Ionic Liquids as New Phases for Supported Organic Synthesis

M. Vaultier, A. Kirschning, and V. Singh

Here we provide a comprehensive review of new task-specific ionic liquids (TSILs) and binary task-specific ionic liquids (BTSILs) as functional ionic liquids designed as alternate soluble supports for supported organic synthesis (SPOS) and combinatorial chemistry. The applications of these supports are based mainly on imidazolium, onium and pyridinium salts. The versatility of the supports has been demonstrated

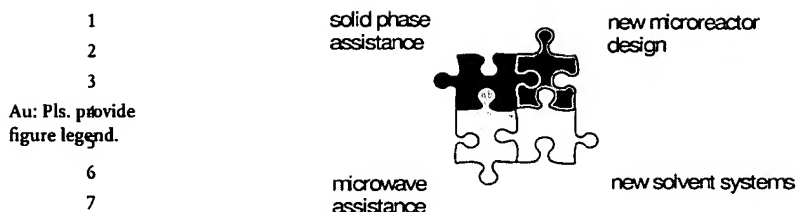


Fig 5.5-1

for the synthesis of small libraries of hetrocyclic compounds, multicomponent reactions, coupling reactions, peptide synthesis, sulfonamide preparations and multistep synthesis of sulfonlated tyrosine derivatives, to mention a few. The use of both ionic liquids and molecular solvents as reaction media is possible. Support recycling, high loading, reaction monitoring by HPLC,  $^1\text{H}$ NMR and GC/MS are some of the significant advantages of this method. Further, a lab on a chip system using task-specific ionic liquids which is based on using an ionic liquid droplet as an e-microreactor has been developed for solution phase synthesis.

### 5.5.1

#### Introduction

Organic synthesis seems to have become so very advanced that basically every molecular target, however structurally complex it may be, can be addressed. However, many developments from research laboratories lack practicality with respect to scale-up, easy and rapid work-up and product isolation, as well as recyclability of precious catalysts. There is a quest to combine new synthetic methodologies with new techniques termed "enabling technologies for organic synthesis" which has been devised to facilitate organic synthesis [1] and hence allow more rapid incorporation into industrial processes [2]. Typical enabling technologies are microwave assistance [3], new solvent systems such as ionic liquids [4], continuous flow reactors [5] and immobilization of chemically active species such as reagents and homogeneous catalysts [6], all of which have recently seen widespread application in research laboratories. Truly new synthetic technology platforms, however, will not be based on the individual use of these new techniques but will require the integration of two or more of these enabling techniques (Fig. 5.5-1).

Solid phase peptide synthesis, as described by Merrifield in 1963 [7], has opened the way for supported organic synthesis as a widely employed technique facilitating the preparation of a large number of compounds. These techniques lie behind combinatorial chemistry and library synthesis. Solid supports such as cross-linked polystyrene beads have been widely used [8]. The success of this approach relies mostly on the ease of product purification and isolation, usually by simple operations such as washing and filtration, which makes automation possible. At the

1 same time, the heterogeneous nature of these polymers gives rise to a number of  
2 problems, including nonlinear reaction kinetics, solvation problems, difficult ac-  
3 cess to reaction sites, slow reaction rates, difficulties in the monitoring reactions,  
4 just to mention a few. Another severe drawback is the low loading of these resins,  
5 typically in the range of 1 mmol g<sup>-1</sup> or less. These limitations have led to alter-  
6 native methodologies tending to restore homogeneous reaction conditions. Thus,  
7 soluble polymer supports such as polyethylene glycols (PEGs), polyvinyl alcohol,  
8 soluble polystyrene [9] and dendritic polyglycerols [10] have attracted much atten-  
9 tion in recent years. Since these are soluble in commonly used molecular solvents,  
10 reactions can be carried out under solution phase conditions. Purification of the  
11 functionalized support, usually by precipitation and filtration, is still an easy process.  
12 Nevertheless, some limitations still exist including a low loading capacity (usually  
13  $\ll$  mmol g<sup>-1</sup>), aqueous solubility, insolubility in ether solvents, retention of solvent  
14 traces, and interference of the PEG framework with certain reagents eventually  
15 leading to degradation. Fluorous solvents and tags have also been successfully used  
16 along these lines [11].

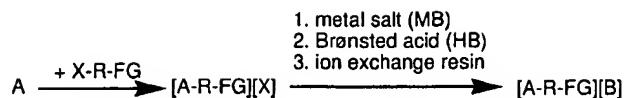
17 Interest in ionic liquids is growing exponentially owing to their many interesting  
18 properties [12]. In the above context, TSILs are of particular importance as they  
19 combine new solvent systems with features of solid phase chemistry. Task specific  
20 ionic liquids have been defined as ionic liquids bearing a functional group covalently  
21 tethered either to the cation or the anion or both. This concept was introduced by J.  
22 Davis Jr. and Wierbicki [13] in 2000 following the demonstration that a thiazolium IL  
23 could interact specifically with a solute and function both as a solvent and a catalyst  
24 for the benzoin condensation [14]. The idea was that the incorporation of one or  
25 several functional groups into the ions of an ionic liquid should confer special  
26 properties or reactivities upon them such as the capacity to behave as reagents,  
27 catalysts or new reaction media [15]. This extends to binary ionic liquids (BILs)  
28 resulting from the addition of ionic solutes such as functional onium salts which do  
29 not have to be liquids at temperature below 100 °C but introduce functional groups  
30 thus conferring some special property to the liquid. These binary task specific  
31 ionic liquids (BTSILs) therefore constitute another family of TSILs. These concepts  
32 proved to be extremely fruitful and are under active investigation in a number of  
33 research groups and a large part of the work in this area has been reviewed by Davis  
34 [16]. The idea of specifically designing either simple TSILs or BTSILs in order to  
35 use them as phases for SPOS arose in the groups of Bazureau [17] and Vaultier  
36 [18] in early 2000. Several groups are now involved in this area. TSILs have been  
37 demonstrated to be very efficient phases for SPOS.

#### 40 5.5.2

#### 41 Synthesis of TSILs

42  
43 TSILs used as soluble supports usually contain functionalized cations. There are  
44 several ways to incorporate functionality into an ionic structure. The most widely  
45 used method relies on the alkylation of a nucleophile such as a tertiary amine,

## 490 | 5 Organic Synthesis



A = amine, heterocycle, phosphine, arsine, thioether

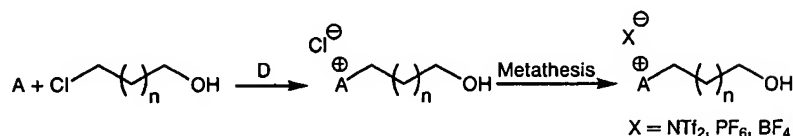
X = leaving group (halide, sulfonate, ...)

R = linker

FG = functional group

B =  $\text{BF}_4^-$ ,  $\text{PF}_6^-$ ,  $\text{NTf}_2^-$ ...M =  $\text{Ag}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Li}^+$ ...

Scheme 5.5-1



Scheme 5.5-2



heterocycle or a phosphine by a bifunctional organic molecule typically bearing an organic halide at one end and the desired functional group at the other, provided that the nucleophilic reagent does not interfere with the functional group. Once the initial onium salt is isolated and purified, anion metathesis is performed to pair the functional cation with an appropriate anion leading to the TSIL. The most widely used techniques for this exchange of anions are the reaction of the onium halides with a silver, sodium, potassium or lithium salt in an appropriate solvent, such as water or acetonitrile, or with a concentrated aqueous solution of the acid, provided that the desired TSIL is only poorly, or not at all, miscible with water (Scheme 5.5-1) [16, 19].

### 5.5.2.1 Synthesis of TSILs Bearing a Hydroxy Group

The hydroxy group is one of the most useful functions for anchoring via esterification or alkylation, to mention but two possibilities. The methodology described in Scheme 5.5-1 has been widely used for the preparation of several  $\omega$ -hydroxylated onium salts according to Scheme 5.5-2. Simply heating a mixture of the nucleophile and the  $\omega$ -chloroalcohol in acetonitrile [18] or without added solvent under microwave irradiation [20] led to the onium chlorides in very good yields. Anion metathesis with aqueous  $\text{H}[\text{PF}_6]$  or  $\text{H}[\text{BF}_4]$  [18] or  $\text{K}[\text{PF}_6]$  or  $[\text{NH}_4][\text{BF}_4]$  [19] in acetonitrile gave the desired TSILs. Triflimides have been obtained by exchange with  $\text{Li}[\text{NTf}_2]$  in water and isolated by simple decantation. Some examples are given in Table 5.5-1. Based on this sequence, so-called poly(ethylene glycol) ionic liquid phases based on imidazolium cations have been prepared in good yields [20].



Table 5.5-1 Synthesis of  $\omega$ -hydroxylated onium salts

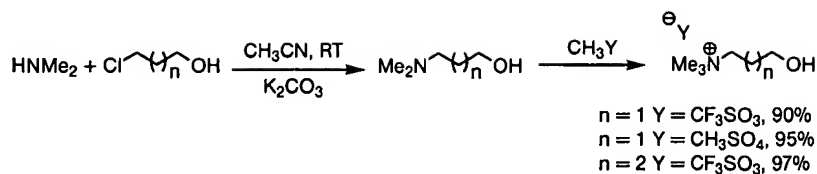
Entry	A	n	X <sup>-</sup>	yield (%)	Ref.
1	MIM <sup>[a,b]</sup>	0	Cl <sup>-</sup>	98	[17]
2	MIM <sup>[c]</sup>	0	[BF <sub>4</sub> ] <sup>-</sup>	85	[17]
3	MIM <sup>[b,c]</sup>	1	Cl <sup>-</sup>	94	[18, 20]
4	MIM <sup>[c]</sup>	1	[PF <sub>6</sub> ] <sup>-</sup>	90	[19]
5	MIM <sup>[c]</sup>	1	[NTf <sub>2</sub> ] <sup>-</sup>	90	[18]
6	NMe <sub>3</sub> <sup>[c]</sup>	0	[NTf <sub>2</sub> ] <sup>-</sup>	90	[18]
7	NMe <sub>3</sub> <sup>[d]</sup>	1	Cl <sup>-</sup>	82	[18]
8	NMe <sub>3</sub> <sup>[e]</sup>	1	[PF <sub>6</sub> ] <sup>-</sup>	67	[18]
9	NMe <sub>3</sub> <sup>[f]</sup>	1	[BF <sub>4</sub> ] <sup>-</sup>	82	[18]
10	NMe <sub>3</sub> <sup>[c]</sup>	1	[NTf <sub>2</sub> ] <sup>-</sup>	86	[18]
11	NMe <sub>3</sub> <sup>[g]</sup>	2	Cl <sup>-</sup>	94	[21]
12	NMe <sub>3</sub> <sup>[c]</sup>	2	[NTf <sub>2</sub> ] <sup>-</sup>	86	[21]
13	NMe <sub>3</sub> <sup>[h]</sup>	3	Cl <sup>-</sup>	62	[21]
14	NMe <sub>3</sub> <sup>[c]</sup>	3	[NTf <sub>2</sub> ] <sup>-</sup>	93	[21]
15	PBu <sub>3</sub> <sup>[c]</sup>	1	Cl <sup>-</sup>	72	[18]
16	PBu <sub>3</sub> <sup>[c]</sup>	1	[NTf <sub>2</sub> ] <sup>-</sup>	90	[18]
17	 N <sup>[i]</sup>	1	Cl <sup>-</sup>	73	[18]
18	 N <sup>[c]</sup>	1	[NTf <sub>2</sub> ] <sup>-</sup>	90	[18]

<sup>a</sup>mp 86–88 °C.<sup>b</sup>MW heating has been used.<sup>c</sup>liquid at RT.<sup>d</sup>mp 158–160 °C.<sup>e</sup>mp 124–126 °C.<sup>f</sup>mp 110–112 °C.<sup>g</sup>mp 118–120 °C.<sup>h</sup>mp 178–180 °C.<sup>i</sup>mp 68–70 °C.

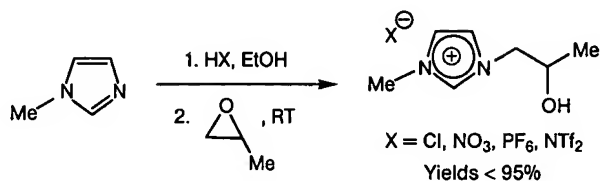
The alkylation step with functionalized alkylating agents is sometimes troublesome, leading to impure salts. Since it is not easy to purify liquid or even solid organic salts, it could be advantageous to synthesize the  $\omega$ -amino alcohols first, which, in principle, are easy to get pure, and then alkylate with simple alkylating agents. This also brings other advantages: first, by using simple alkyl sulfonates or sulfates, halogen-free ionic liquids can be obtained and second, these ionic liquids can be prepared *in situ* under water-free conditions. This is illustrated by the following examples (Scheme 5.5-3) [21].

Several other methodologies have been employed for the synthesis of hydroxylated TSILs. 2-Hydroxypropyl-functionalized imidazolium salts have been prepared in excellent yields by the reaction of protonated 1-methylimidazole with propylene oxide, the acid providing the anionic component of the resultant ionic liquid (Scheme 5.5-4) [22].

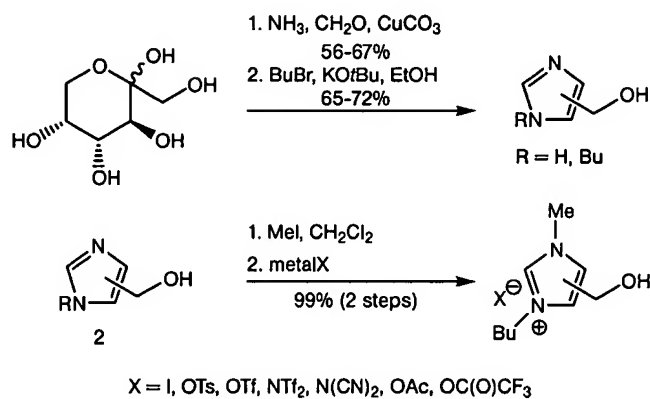
## 492 | 5 Organic Synthesis



Scheme 5.5-3



Scheme 5.5-4



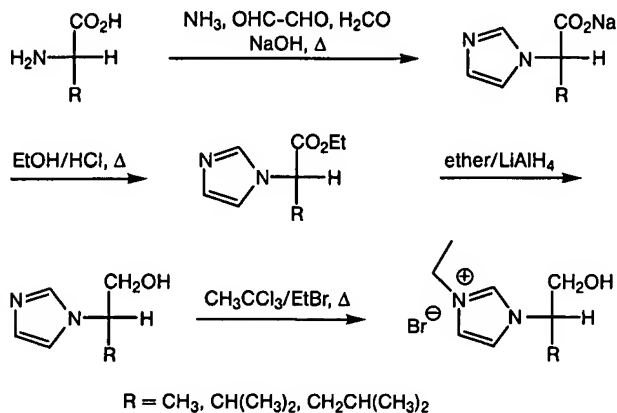
Scheme 5.5-5

Fructose can be readily transformed into hydroxymethylene-imidazole according to a reaction developed by Trotter and Darby [23]. Alkylation leads to imidazolium cations (Scheme 5.5-5) [24].

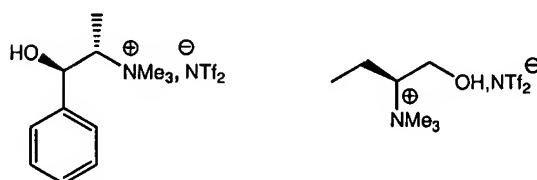
Chiral  $\beta$ -hydroxyimidazolium salts containing one chiral carbon in the  $\alpha$ -position to the imidazolium ring have been synthesized from natural  $\alpha$ -aminoacids (Scheme 5.5-6) [25].

Ionic liquids derived from the alkaloid ephedrine or (*S*)-valinol have been readily obtained on a kilogram scale in a three-step synthesis: a Leuckart-Wallach reaction followed by alkylation with  $\text{Me}_2\text{SO}_4$  and ion exchange in aqueous solution (Scheme 5.5-7) [26].

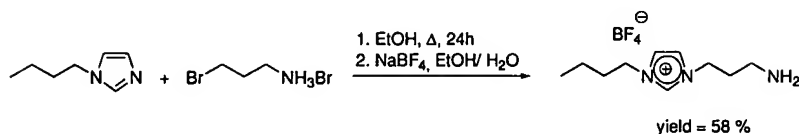
In principle, any  $\omega$ -functionalized alkylating agent could be used for the quaternization of a tertiary amine or phosphine, provided that the alkylation reaction



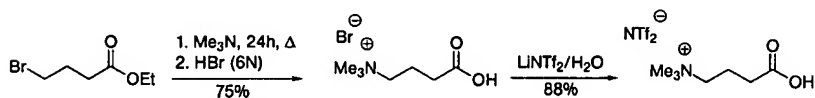
Scheme 5.5-6



Scheme 5.5-7



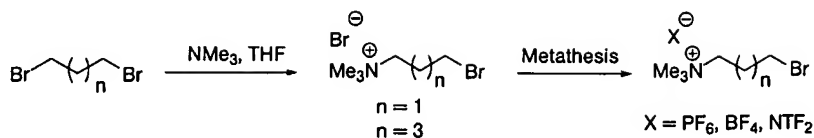
Scheme 5.5-8



Scheme 5.5-9

is chemoselective and the alkylating agent stable under the alkylation conditions. Several examples, selected for their potential to give further functionalized ionic liquids and therefore serve as soluble supports, are reported below including: ionic liquids bearing a primary amino group (Scheme 5.5-8) [27] a carboxylic function (Scheme 5.5-9) [21] or a bromine (Scheme 5.5-10) [21].

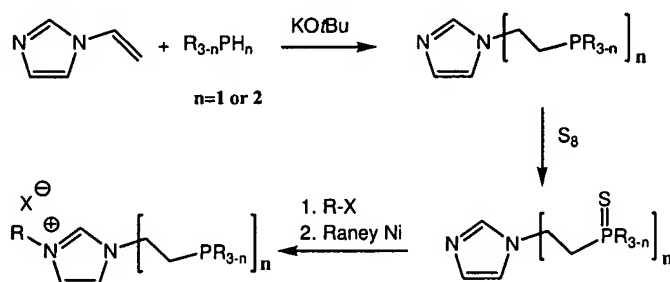
## 494 | 5 Organic Synthesis



Scheme 5.5-10

Table 5.5-2 Synthesis of  $\omega$ -bromoalkyl trimethylammonium salts [18, 21].

Entry	$n$	$\text{X}^-$	Yield (%)	Mp ( $^\circ\text{C}$ )
1	1	$\text{Br}^-$	99	212–214
2	1	$[\text{PF}_6]^-$	88	144–146
3	1	$[\text{NTf}_2]^-$	86	liquid
4	3	$\text{Br}^-$	96	138–140
5	3	$[\text{NTf}_2]^-$	84	liquid
6	3	$[\text{PF}_6]^-$	97	138–140
7	3	$[\text{BF}_4]^-$	78	liquid



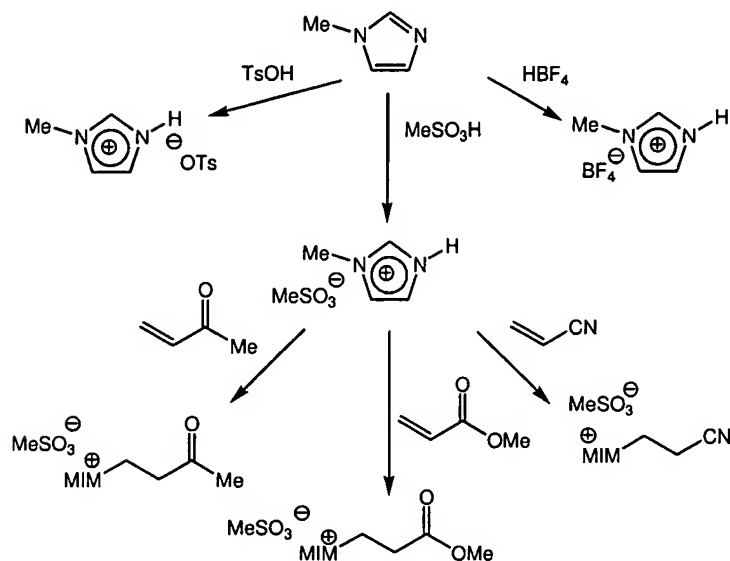
Scheme 5.5-11

Several  $\omega$ -bromoalkyltrimethylammonium salts have been prepared in good yields according to Scheme 5.5-10 (Table 5.5-2). These salts are well suited for further transformations into other TSILs bearing an amino group, for example.

A roundabout strategy may be necessary in a number of cases where the alkylation step is not compatible with the electrophilic reagent used, thus making protective groups necessary. A good example of this kind of methodology is the synthesis of imidazolium substituted mono or bis-phosphines from 1-vinylimidazole (Scheme 5.5-11) [28].

#### 5.5.2.2 Parallel Synthesis of Functionalized ILs from a Michael-type Reaction

A very efficient alternative method for the synthesis of functionalized ionic liquids in a simple two-step process has been proposed by Wasserscheid et al. [29]. In this approach, the imidazole or the required nucleophile is protonated by the acid whose anion will be incorporated into the final ionic liquid. A Michael acceptor,



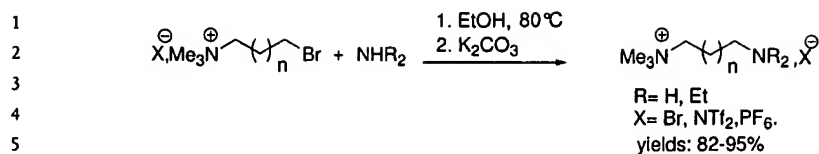
Scheme 5.5-12

which inserts into the N–H or Nu–H bond, is added to the resultant salt. This approach is widely applicable, leading to TSILs in excellent yields (Scheme 5.5-12). It is notable that there is no need for extraction, filtration or further anion metathesis steps. Since no by-product is formed, the two-step sequence proceeds with perfect atom economy. This methodology allows for the rapid parallel synthesis of libraries of TSILs in a combinatorial fashion (this has been realized with three amines, three carboxylic acids and five Michael acceptors). Another interesting feature of this new synthesis is its potential for large-scale production of cheap industrial ionic liquids since several amines or nitrogen heterocycles, acids and Michael acceptors are produced on a large scale. Substituted acrylates such as methyl methacrylate or cinnamate were not as reactive, leading to incomplete reactions or no reaction at all. Thermal stability might be a concern since the Michael-type addition reaction was found to be reversible at higher temperature. This drawback could be circumvented by further functional group transformations.

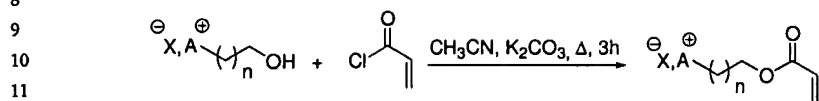
### 5.5.2.3 Synthesis of TSILs by Further Functional Group Transformations

Several functional group transformations that lead to new TSILs starting from hydroxyl-, carboxylic acid, hydroxyl-, amino- or halo-substituted TSILs are possible. Primary, secondary and tertiary amines have been prepared in very good yields from the corresponding  $\omega$ -bromo derivatives by nucleophilic substitution according to Scheme 5.5-13 [21]. Primary and secondary amines can be further used to graft other functional groups and, therefore, act as soluble supports, as we will see later. Tertiary amines can serve as supported bases or ligands.

## 496 | 5 Organic Synthesis




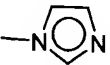
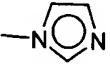

Scheme 5.5-13



Scheme 5.5-14

Table 5.5-3 Synthesis of TSILs bearing an acrylic ester [21]

13  
14  
15  
16  
17  
18

Entry	A (or A <sup>+</sup> )	n	X	Yield (%) <sup>[a]</sup>
19 1	NMe <sub>3</sub>	1	[NTf <sub>2</sub> ] <sup>-</sup>	90
20 2	NMe <sub>3</sub>	2	[NTf <sub>2</sub> ] <sup>-</sup>	98
21 3	NMe <sub>3</sub>	2	Br	98
22 4	NMe <sub>3</sub>	2	[BF <sub>4</sub> ] <sup>-</sup>	93
23 5	NMe <sub>3</sub>	2	[PF <sub>6</sub> ] <sup>-</sup>	90 <sup>b</sup>
24 6	NMe <sub>3</sub>	3	[NTf <sub>2</sub> ] <sup>-</sup>	77
25 7	NMe <sub>3</sub>	5	[NTf <sub>2</sub> ] <sup>-</sup>	78
26 8	PBu <sub>3</sub>	2	[NTf <sub>2</sub> ] <sup>-</sup>	77
27 9		2	[NTf <sub>2</sub> ] <sup>-</sup>	80
28 10		2	[NTf <sub>2</sub> ] <sup>-</sup>	85
29 11 (Ref. [30])		1	[PF <sub>6</sub> ] <sup>-</sup>	98
30 12 (Ref. [31])		0	[NTf <sub>2</sub> ] <sup>-</sup>	96

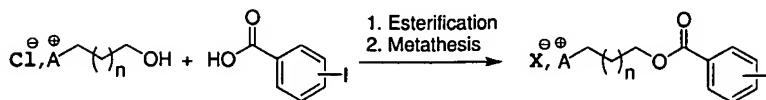
31  
32  
33  
34  
35

36 <sup>a</sup>Oils at RT. Yields are for isolated pure compounds.

37 <sup>b</sup>mp = 70–72 °C.

38  
39  
40 The ester link has been extensively used to graft new functional molecules. Acrylic  
41 esters linked to onium cations via a spacer have been obtained in excellent yields  
42 and purity by simple acylation with acryloyl chloride or esterification with acrylic  
43 acid of the ω-hydroxyl TSILs under standard conditions (Scheme 5.5-14).

44 Powdered potassium carbonate proved to be an efficient base to remove HCl from  
45 the reaction mixture. Some examples are reported in Table 5.5-3.



Scheme 5.5-15

Table 5.5-4 Synthesis of 4-iodobenzoic esters

Entry	A	Nn	X	Yield (%)	mp (°C)
1	NMe <sub>3</sub>	0	Cl	93	258–260
2	NMe <sub>3</sub>	0	[BF <sub>4</sub> ] <sup>−</sup>	90	200–202
3	Me-N <sup>+</sup> (Me) <sub>2</sub>	0	Br	92	228–230
4	Me-N <sup>+</sup> (Me) <sub>2</sub>	0	[BF <sub>4</sub> ] <sup>−</sup>	85 <sup>b</sup> [33]	146–148
5	NMe <sub>3</sub>	1	Cl	95	218–220
6	NMe <sub>3</sub>	1	[BF <sub>4</sub> ] <sup>−</sup>	83	190–192
7	NMe <sub>3</sub>	1	[NTf <sub>2</sub> ] <sup>−</sup>	95 <sup>b</sup> [21]	48–50
8	NMe <sub>3</sub>	4	[BF <sub>4</sub> ] <sup>−</sup>	87	170–172
9	NMe <sub>3</sub>	1	[NTf <sub>2</sub> ] <sup>−</sup>	88	78–80

<sup>a</sup>Yields are for isolated pure salts.

<sup>b</sup>The 3-iodo benzoic ester has also been prepared.

The acrylic moiety has been grafted onto more complicated ionic liquid phases called poly(ethyleneglycol)ionic liquid phases (PEG<sub>n</sub>-ILPs). 3- and 4-Iodobenzoic esters have also been grafted by an esterification of the corresponding benzoic acid, performed in the presence of the coupling mixture DCC/DMAP. Excellent results were obtained provided that the dicyclohexylurea formed as a by-product is properly removed (Scheme 5.5-15). It is worth noting that all these salts are high melting compounds that are easy to purify by recrystallisation, and they cannot be called [32] ionic liquids. Nevertheless, they have proved to be very useful as part of BTSILs and should be included here [21].

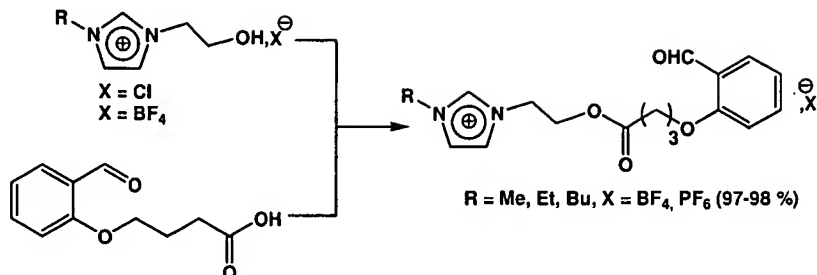
Several examples are reported in Table 5.5-4. These esters are well suited for Heck and Suzuki-Miyaura coupling reactions.

Sophisticated functionalized ionic liquids aimed at supporting 2-hydroxybenzaldehyde have been prepared by esterification of 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate (Scheme 5.5-16) [17].

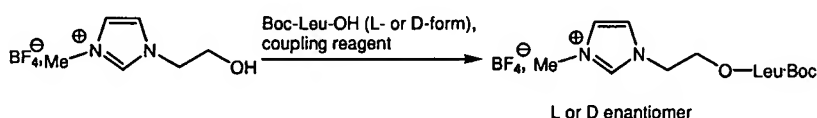
Natural α-aminoacids can also be grafted on to ionic liquids by simple esterification as illustrated in (Scheme 5.5-17) [34].

The esters derived from acetylacetic acid have been realised either from ethylacetoacetate by transesterification with 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate under MW irradiation [35] or by reaction of hydroxyalkyltrimethylammonium salts with a ketene dimer (Scheme 5.5-18) [36].

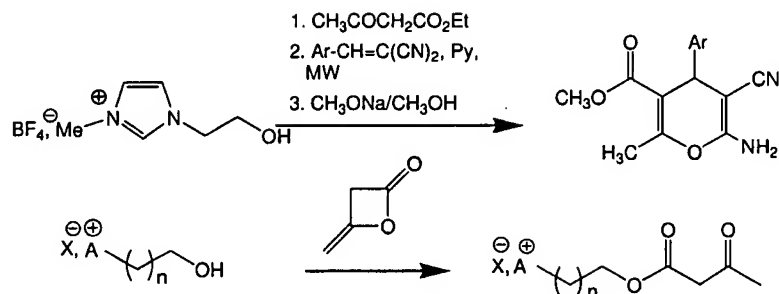
## 498 | 5 Organic Synthesis



Scheme 5.5-16



Scheme 5.5-17



Scheme 5.5-18

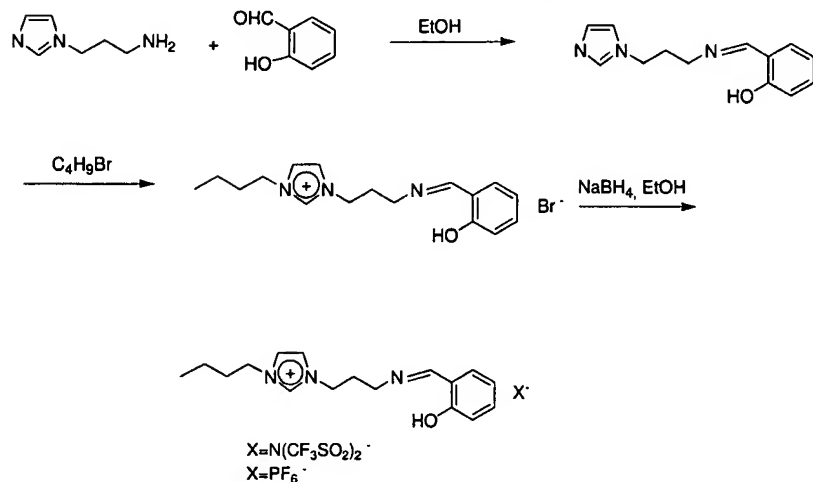
Two new TSILs bearing 2-hydroxybenzylamine based on an imidazolium substructure and used for the extraction of americium ions have been reported by Ouadi et al. [37] (Scheme 5.5-19).

Li et al. [38] have synthesized a series of *N*-ester and *N*-carboxyl appended pyridinium task specific ionic liquids and have found them to be immiscible with acetone and dichloromethane, unlike the imidazolium ionic liquids, and to have improved thermal stability up to 300 °C.

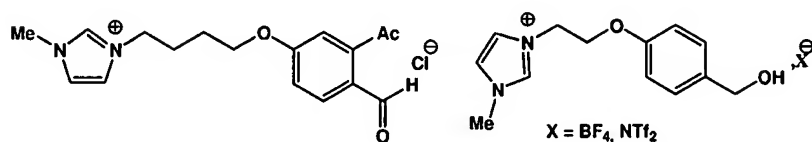
The ether link has also been used to give ionic liquids bearing Wang-type linkers via the Williamson alkylation [39, 40] (Scheme 5.5-20).

From what is reported above, it can be seen that many of the examples of so-called TSILs are either high melting solids, or highly viscous oils or waxes. This leads logically to the extension of the concept of TSILs to that of task-specific onium salts, TSOSs, free from the restriction of being liquid below 100 °C [21]. TSOSs can be useful as soluble supports for solution phase organic synthesis. There are





Scheme 5.5-19



Scheme 5.5-20

three possibilities to be considered. First, if the TSOSs are liquid at or near room temperature, they belong to the first generation of TSILs which rapidly become very viscous or waxes or solids as their functionalization increases and, therefore, become no longer easy to handle. Second, TSOSs can dissolve, whatever their physical state is, i.e. liquid or waxy or crystalline solid, in a non-functionalized ionic liquid which plays the role of a solvent giving BTSILs. The third possibility is to dissolve TSOSs in a molecular solvent and use them as classical soluble supports. These three possibilities have been illustrated in the literature and widen the area of SPOS. It can be safely anticipated that this area is going to expand very rapidly, owing to the interest in these new soluble supports.

#### 5.5.2.4 Loading of TSIL Supports

One of the main limitations of traditional solid or soluble supports is their low loading capacity which is related to the molecular weight of these polymers. Loadings of over  $1 \text{ mmol g}^{-1}$  of polymer are rarely reached. Also, these polymers are used diluted either as suspensions or in solution in some molecular solvent. Then, we should consider the loading of the suspension or the solution that will be used for the reaction to be carried out. Most of the time low loadings such as  $0.1 \text{ mmol g}^{-1}$ ,

## 500 | 5 Organic Synthesis

Table 5.5-5 Loading capacity of the onium salts  $[A-(CH_2)_nOH][X]$ 

A	n	X	Molecular weight	Loading capacity (mmol g <sup>-1</sup> )
MIM <sup>[a]</sup>	2	Cl	146.5	6.82
MIM	2	[NTf <sub>2</sub> ] <sup>-</sup>	391	2.56
Me <sub>3</sub> N	2	Cl	139.5	7.17
Me <sub>3</sub> N	2	[NTf <sub>2</sub> ] <sup>-</sup>	384	2.60
Me <sub>3</sub> N	3	Cl	153.5	6.51
Me <sub>3</sub> N	3	[BF <sub>4</sub> ] <sup>-</sup>	205	4.87
Me <sub>3</sub> N	3	[PF <sub>6</sub> ] <sup>-</sup>	263	3.80
Me <sub>3</sub> N	4	Cl	167.5	5.97
Me <sub>3</sub> N	4	[OTf] <sup>-</sup>	283	3.53
Me <sub>3</sub> N	4	[NTf <sub>2</sub> ] <sup>-</sup>	398	2.51
Me <sub>3</sub> N	6	Cl	181.5	5.50
Me <sub>3</sub> N	6	[NTf <sub>2</sub> ] <sup>-</sup>	426	2.34
—	—	MPEG 5000	5000	0.2

<sup>a</sup> MIM = methylimidazolium cation.

or less, of suspension or solution are common. TSOSs and TSILs are low molecular weight soluble supports, as illustrated by the examples given in Table 5.5-5. It can be seen that chlorides have a high loading capacity, up to more than 7 mmol g<sup>-1</sup>, owing to their low molecular weight, which compares to the loading capacity of MPEG 5000 which is 0.2 mmol g<sup>-1</sup>. It is also worth noting that a one molar solution of MPEG 5000 contains 5000 mg of polymer per ml of solution, which is not realistic as compared to 139.5 mg for choline chloride.

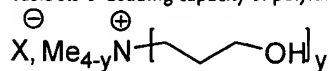
The loading capacity of the TSOSs and TSILs can be easily increased by using polyfunctional cations. For example, an ammonium cation can be substituted by at most four functional substituents. These kind of multifunctional salts have been prepared [18, 21] and their loading capacity is reported in Table 5.5-6. This loading capacity could even be increased by dendrimerization if necessary [10].

## 5.5.3

## TSILs as Supports for Organic Synthesis

Combinatorial chemistry is a powerful tool for the generation of libraries of compounds for the screening of functional molecules. Solid-phase organic synthesis (SPOS) is an efficient method for high-throughput synthesis which exhibits several shortcomings, such as the heterogeneous nature of the reaction and difficulties in reaction monitoring. By using soluble polymer supports, the familiar reaction conditions of organic chemistry in solution are reinstated, and yet product purification is still facilitated. However, the low loading capacity is the main limitation. So, a search for alternative soluble supports for high-throughput organic synthesis is necessary. In recent years, there has been more attention focused on the TSILs as soluble supports. RTILs have a number of interesting physical and chemical

Table 5.5-6 Loading capacity of polyfunctional TSILs [21]



Entry	y	X	Molecular weight	Loading capacity mmol g <sup>-1</sup> (mf g <sup>-1</sup> )
1	2	Cl <sup>-</sup>	197.75	5.05 (10.11)
2	2	[NTf <sub>2</sub> ] <sup>-</sup>	442.25	2.26 (4.54)
3	3	Cl <sup>-</sup>	241.80	4.13 (12.4)
4	3	[NTf <sub>2</sub> ] <sup>-</sup>	486.30	2.05 (6.17)
5	4	Cl <sup>-</sup>	285.85	3.50 (14)
6	4	[NTf <sub>2</sub> ] <sup>-</sup>	530.35	1.88/7.51

\*mf g<sup>-1</sup> represents the number of millifunctions/g of support (mf g<sup>-1</sup> = mmol g<sup>-1</sup> · y).

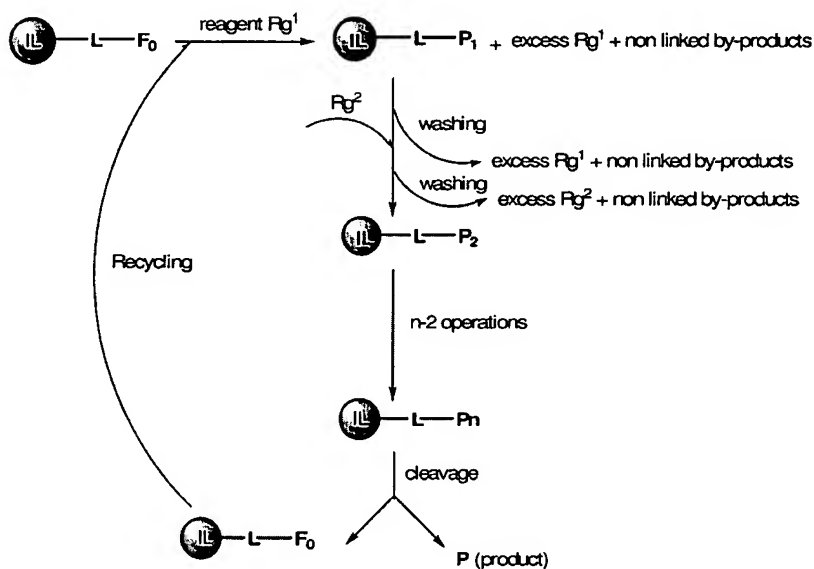


Fig 5.5-2

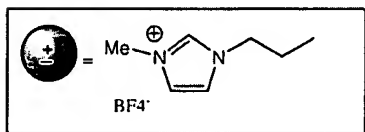
properties which have been discussed in other chapters. Some of them are essential for the development of new soluble supports including thermal and chemical stabilities, insignificant vapor pressure, non-flammability, tuneable solubility. Supporting catalysts in RTILs in order to immobilise them in one liquid phase of a biphasic system has led to interesting developments over the last few years [39–41]. Less effort has been spent on supported non-metallic reagents [42]. The general concept of ionic liquid supported synthesis is shown in Fig. 5.5-2.

The TSIL used as a support is drawn like a solid support, i.e. the function  $F_0$  used as the anchor point is linked to the ionic head via a linker which can be more or less sophisticated. Results from the literature show that using sophisticated linkers, such as those described for solid phase supported synthesis is not necessary and moreover could bring additional problems. Grafting of the first reagent  $R_1$  leads to a new TSIL where  $F_0$  has been transformed into  $P_1$  which is mixed with an excess of reagent used for the first chemical transformation and eventually by-products. This excess reagent and non-linked by-products can be removed by washing with an appropriate solvent, or by stripping under high vacuum and heating, or by other separation techniques. The resulting purified TSIL can then be further functionalized. It is notable that it is usually very easy to follow the reactions by standard spectroscopic techniques, such as high-resolution NMR, FTIR, UV etc. and/or by chromatographic methods such as HPLC or TLC. This is a definite advantage over the classical Merrifield-type resins or polymeric soluble supports. After several transformations, the desired product  $P$  is liberated from the support by cleavage and can be separated from the starting TSIL in classical ways such as extraction with a non-miscible solvent, bulb to bulb distillation under high vacuum, column chromatography etc. Then, the starting TSIL can be recycled. At the moment, two distinct kinds of TSILs have been developed and reported in the literature: a first generation of pure functionalized ionic liquids and a second one which is based on binary functionalized ionic liquids or BTSILs.

#### 5.5.3.1 First Generation of TSILs as New Phases for Supported Organic Synthesis

TSILs derived from 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate or hexafluorophosphate have been used in Knoevenagel reactions, 1,3-dipolar cycloadditions [17] synthesis of 4-thiazolidinones [43] and 2-thioxotetrahydropyrimidin-4-(1H)-ones [30] under focused microwave irradiation. Under these conditions, Knoevenagel reactions with malonate derivatives catalyzed by 2% piperidine are over after a short reaction time (15–60 min) at 80 °C. Washing of the TSIL obtained with AcOEt or Et<sub>2</sub>O was followed by cleavage with sodium methanolate in methanol. After removal of solvent *in vacuo*, the expected compounds were extracted with CH<sub>2</sub>Cl<sub>2</sub> and isolated in 87–98% yields without the need for silica gel chromatography. The starting TSIL could eventually be recovered and reused in another cycle of the synthesis (Scheme 5.5-21).

Benzaldimines have been obtained from the same supported benzaldehyde and various alkylamines in short reaction times (20 min) and good yields. A regioselective 1,3-dipolar cycloaddition with an imidate derived from dimethylaminomalonate led to a cycloadduct, treatment of which with 10% NaOMe in MeOH resulted in the diethyl 2-imidazoline-4,4-dicarboxylate in 84% yield. These two examples show clearly the interest and the simplicity of this methodology. Product isolation in a good state of purity necessitates only an extraction, because non-linked side-products have been removed by simple washing of the TSILs. No chromatography was necessary. Standard analytical methods (NMR, TLC) can be used to monitor reaction progress. This methodology has been extended to the parallel synthesis of some heterocycles. Condensation of  $\alpha$ -mercaptopcarboxylic acids with the supported

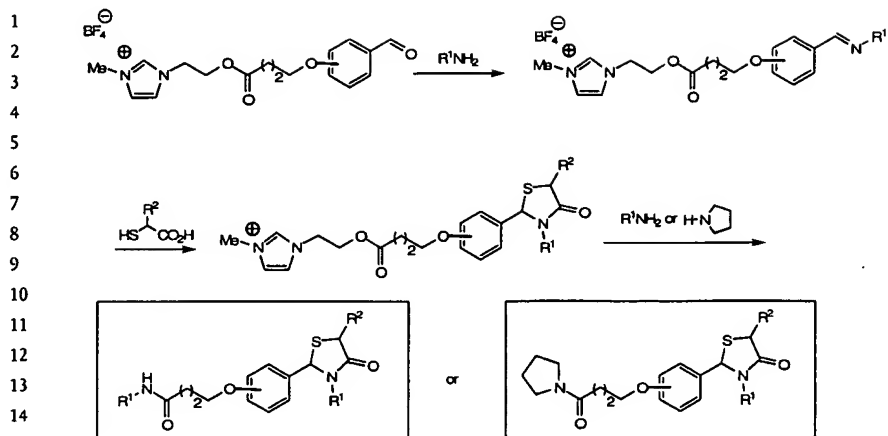


**Scheme 5.5-21**

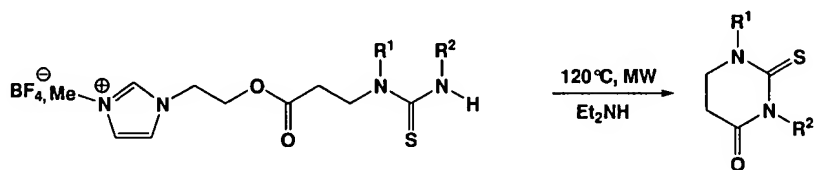
imines gave 4-thiazolidinones in 12–86% conversion. Ester aminolysis with primary or secondary amines catalysed by <sup>t</sup>BuOK under MW heating led to 4-thiazolidinones in modest overall yields ranging from 25 to 61% after purification by extraction and flash chromatography (Scheme 5.5-22) [41]

MW heating of supported thioureas  $\omega$ -substituted by an ester function used as a grafting element to the imidazolium moiety in the presence of diethylamine

## 504 | 5 Organic Synthesis



Scheme 5.5-22



Scheme 5.5-23

25

26

27 led to free 2-thioxotetrahydropyrimidin-4(1H)-ones by an intramolecular

28 cyclisation–cleavage sequence in good yields (67–85%) after flash chromatography

29 (Scheme 5.5-23) [30].

30 Reaction of IL-bound acetoacetate with excess arylidenemalononitriles under

31 MW irradiation gave bound 4-H pyranes. Excess reagent could be removed

32 by simple washing. Cleavage by sodium methoxide in methanol (monitored

33 by TLC) gave methyl-6-amino-5-cyano-4-aryl-2-methyl-4H-pyran-3-carboxylates in

34 good yields (85–91%) and purities (85–99%) without further purification (Scheme

35 5.5-24). The recovered IL after cleavage can be simply reused in a second run.

36 According to the authors, but not described, the methodology is compatible with

37 automatic manipulation [35].

38 Supported liquid acrylic esters have been prepared from hydroxylated

39 imidazolium-based TSILs and used neat in (4+2) Diels-Alder cycloadditions. First,

40 Handy et al. [31] used a fructose-derived ionic liquid to support acrylic acid and

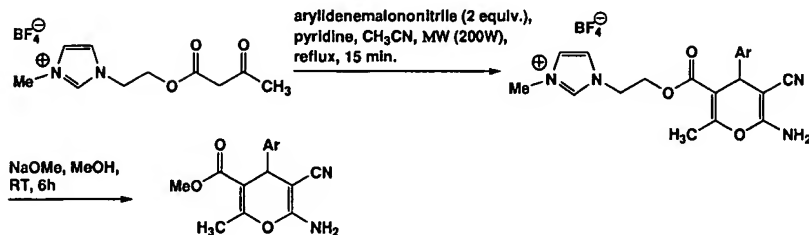
41 performed the Diels-Alder cycloaddition with several dienes including cyclopenta-

42 and cyclohexadienes and butadiene derivatives at 120 °C for 12 h in the presence of

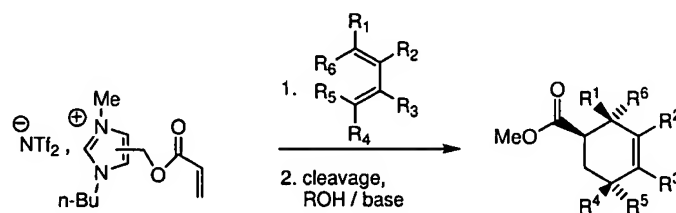
43 hydroquinone (Scheme 5.5-25).

44 Excess diene and other volatiles were removed *in vacuo* and the supported cy-

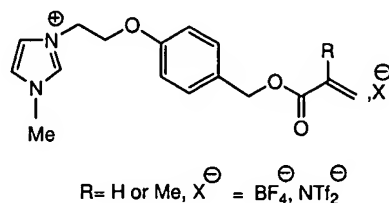
45 cloadducts washed with cyclohexane. Transesterification with MeOH or EtOH



Scheme 5.5-24



Scheme 5.5-25

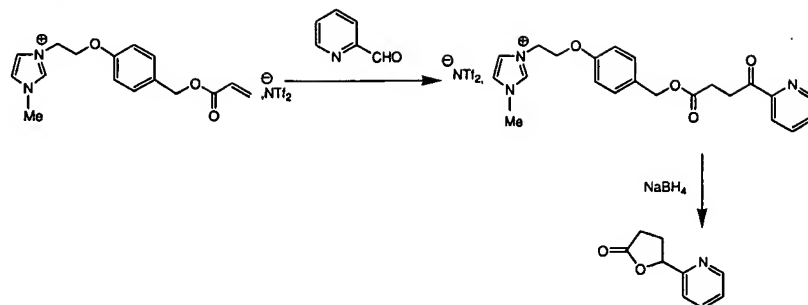


Scheme 5.5-26

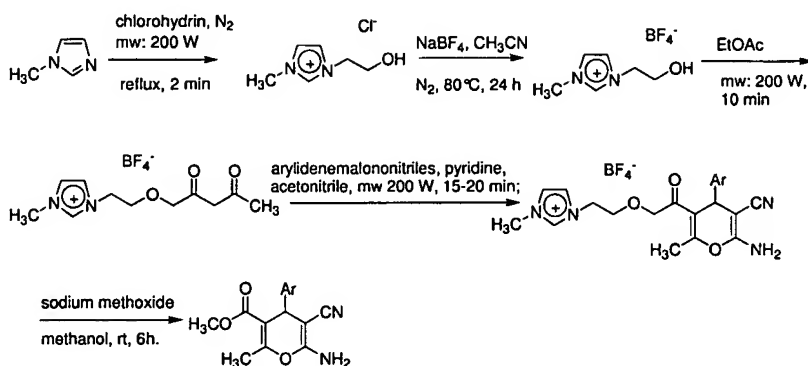
31 under basic conditions appeared to be troublesome, because of the ease of deprotonation of the imidazolium cation at the 2-position and led to a dark brown viscous liquid. The most effective transformation was the cyanide-mediated transesterification in methanol leading to the methyl esters of the corresponding cycloaddition adducts in good overall yields (46–63% for the 3-step sequence). Ethyl and benzyl esters also could be obtained using this methodology. The ionic support was readily recycled. More complicated linkers have been used by Grée et al. [38] to support acrylic esters on imidazolium derived ionic liquids via a Wang-type linker (Scheme 5.5-26).

40 Again, good results were obtained, but nothing was said about the recycling protocol of the IL support. The use of a complex linker does not seem to be a limiting addition, unlike the former system. These acrylic esters have also been used as partners in several other reactions such as 1–4 additions of nucleophiles such as pyrrolidine or thiophenol in the presence of  $\text{Et}_3\text{N}$ , Heck coupling and dihydroxylation of the obtained cinnamic esters. Methyl esters could be isolated in

## 506 | 5 Organic Synthesis



Scheme 5.5-27



Scheme 5.5-28

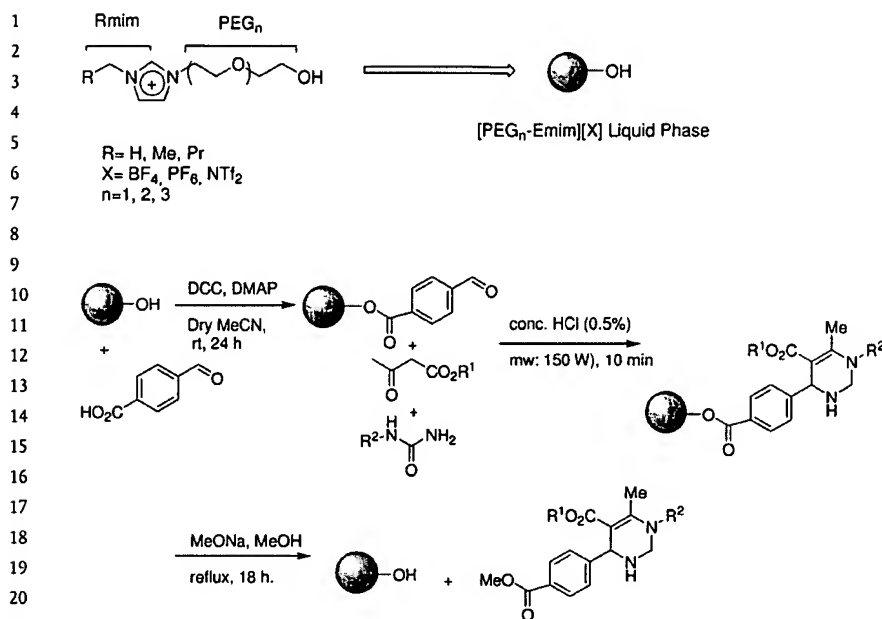
good yields after transesterification with methanol under basic conditions. Finally, the Stetter reaction of pyridine-2-carboxaldehyde led to the expected 1,4-dicarbonyl compound (87% yield) which after reduction with sodium borohydride afforded a lactone by a cyclorelease cleavage from the support (50% yield) (Scheme 5.5-27).

The combined effect of microwave heating and functional ionic liquid as soluble support has been demonstrated for the synthesis of methyl 6-amino-5-cyano-4-aryl-2-methyl-4H-pyran-3-carboxylate [44], which are polyfunctionalised 4H-pyrans with pharmacological activity. The ionic liquid bound acetoacetate was treated with various substituted arylidenemalononitriles to give supported 4H-pyran derivatives. After cleavage, the target compounds were obtained in good yields (93–97%) and high purities (99%) without chromatographic purification (Scheme 5.5-28).

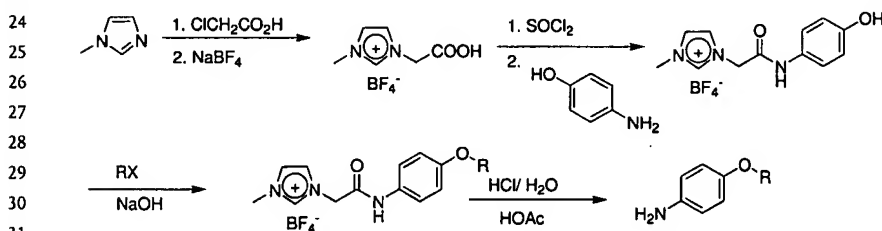
A microwave dielectric heating assisted TSIL phase synthesis [45] of 1,4-dihydropyridines, 3,4-dihydropyrimidin-2(1H)-ones, pyridines and polyhydroquinolines using a TSIL as a soluble support was described. The efficiency of the ionic liquid phase organic synthesis (IoLiPOS) methodology was demonstrated by using a one-pot three-component condensation. The structure of the intermediates in each



## 5.5 Task-specific Ionic Liquids as New Phases for Supported Organic Synthesis | 507



Scheme 5.5-29



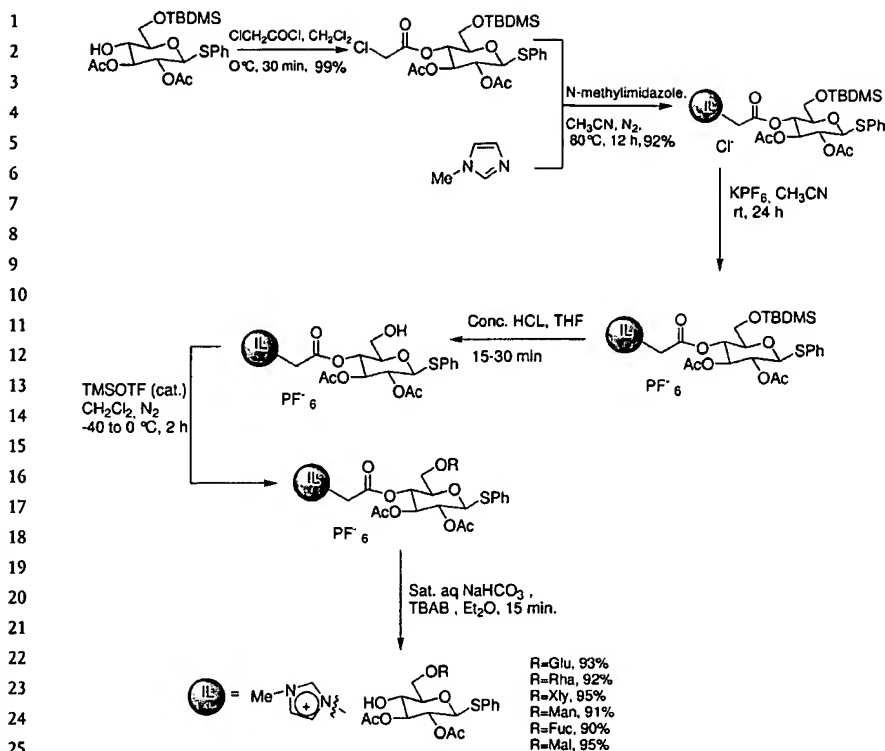
Scheme 5.5-30

step was verified routinely by spectroscopic analysis and, after cleavage the target compounds were obtained in good yields and high purities (Scheme 5.5-29).

Song et al. [46] have used a carboxyl-functionalized ionic liquid [CMMIM][BF<sub>4</sub>] as soluble support to synthesize a small library of 4-aminophenyl ethers via Williamson reaction and extracting with ethyl acetate in good yields (75–80%) and purities (99%). The recovered ionic liquid support was reused several times with consistent loading capacity (Scheme 5.5-30).

Wang et al. [47] have reported a novel and efficient protocol for ionic liquid supported synthesis of oligosaccharides, which have biological and therapeutic importance. This methodology is remarkable for improved phase separation from organic solvent or aqueous phase. The ionic liquid supported oligosaccharides were

## 508 | 5 Organic Synthesis



Scheme 5.5-31

soluble in polar organic solvents such as acetone, chloroform, methanol, and are not soluble in hexane and ether, which made it possible to remove the excess reagent and impurities by simple washing with ether or hexane, providing an attractive alternative to the classical solid- and fluorous-phase synthesis, combining the advantage of performing homogeneous chemistry on a relatively large scale while avoiding large excesses of reagents (Scheme 5.5-31).

A microwave-assisted liquid phase Gewald synthesis [48] of 2-aminothiophenes was developed using the TSIL, 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate, [2-(OH)EMIM][BF<sub>4</sub>] as soluble support. This new synthetic method is simple and efficient, and the products are obtained in good to excellent yields with high purities, without the need for chromatographic purification.

This hydroxy functionalized ionic liquid [49], [2-(OH)EMIM][BF<sub>4</sub>] was prepared under microwave irradiation via methylimidazolium, chlorohydrin and sodium tetrafluoroborate as materials. A microwave assisted solution phase parallel synthesis of 3,4-dihydropyridones was developed using [2-(OH)EMIM][BF<sub>4</sub>] as a soluble support. First, the [2-(OH)EMIM][BF<sub>4</sub>] was reacted with ethyl acetoacetate to obtain IL-bound acetoacetate, then this intermediate was reacted with Meldrum's acid,

1 ammonium acetate and aromatic aldehyde. Finally 3,4-dihydropyridone derivatives  
2 were obtained in good yields and high purities without chromatographic purifica-  
3 tion after mild cleavage with sodium methoxide in methanol at room temperature.  
4 The target compounds had a purity of 95–98% and the yield was 83–93%. The recov-  
5 ered functionalized ionic liquid could be recycled at least six times without losing its  
6 activity. It was clear that the solution phase synthesis using functionalized ionic liq-  
7 uid as supports could be used in the combinatorial synthesis of 3,4-dihydropyridone  
8 derivatives in high efficiency.

9 In summary, these TSILs offer several advantages over the usual supports:

- 10
- 11 • Higher loading capacity is achieved due to the lower molecular weight of the
- 12 functionalized ionic liquid.
- 13 • Since the intermediates can be purified by simple extraction, the desired products
- 14 can be obtained in high yields and purities without further chromatographic
- 15 purification.
- 16 • This methodology can be applied to parallel synthesis and small libraries have
- 17 been prepared.
- 18 • In some cases, depending on the treatment, the recovery of the ionic liquid after
- 19 cleavage is possible and it can be reused in another cycle without losing its activity.
- 20

21

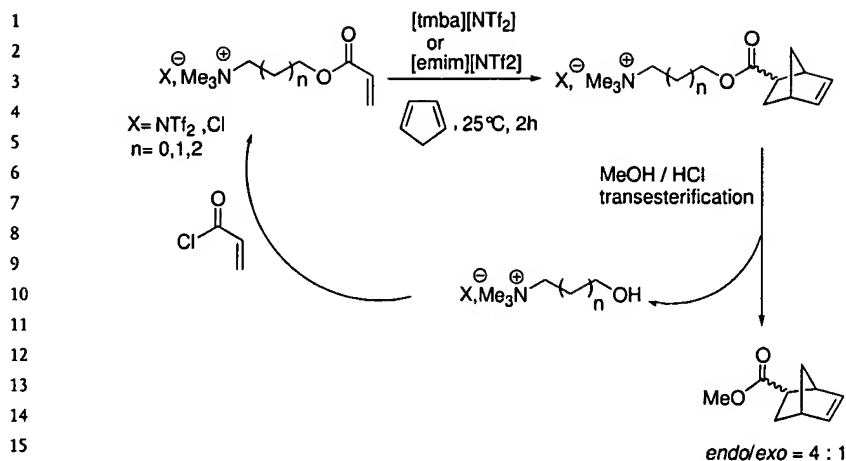
22 At present the key challenges in using this type of support are the limited stability  
23 of the imidazolium cation in the presence of base and the viscosity of these TSILs,  
24 since the more they are substituted the more viscous they become. Therefore, it  
25 is difficult to handle and stir them, necessitating the use of MW for heating, for  
26 example.

#### 27

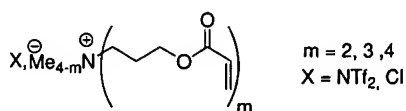
#### 28 5.5.3.2 Second Generation of TSILs: The BTSILs

29 The question of viscosity can be solved by dissolving a functionalized salt (i.e. TSOS)  
30 in a non-functionalized ionic liquid used as a solvent. The viscosity of these binary  
31 mixtures is not sensitive to further functionalization of the TSOS dissolved in the  
32 solvent. Moreover, it is possible to use TSOSs which are high melting onium salts.  
33 Furthermore, these salts can have a cation and (or) an anion different from the  
34 solvent. The only necessity is that the salt itself must be reasonably soluble in the  
35 ionic liquid used as the solvent [21]. This has widened the range of accessible and  
36 useful salts to any functionalized onium salt available by simple organic synthesis  
37 and, therefore, very much broadened the scope of the utilization of TSILs as soluble  
38 supports. The limited stability of the imidazolium cation in the presence of base  
39 could also be largely solved by using tertiary ammonium or phosphonium cations  
40 either for the IL solvent or the TSOSs. These cations also offer a better chemical sta-  
41 bility towards basic, reducing, oxidizing and nucleophilic reagents. Many different  
42 kinds of reactions have been looked at using BTSILs as soluble supports, includ-  
43 ing Diels-Alder cycloadditions, C–C bond formation by coupling reactions (Heck,  
44 Suzuki-Miyaura, Sonogashira), multicomponent reactions, and peptide synthesis  
45 [18,21,44–60].

## 510 | 5 Organic Synthesis



Scheme 5.5-32

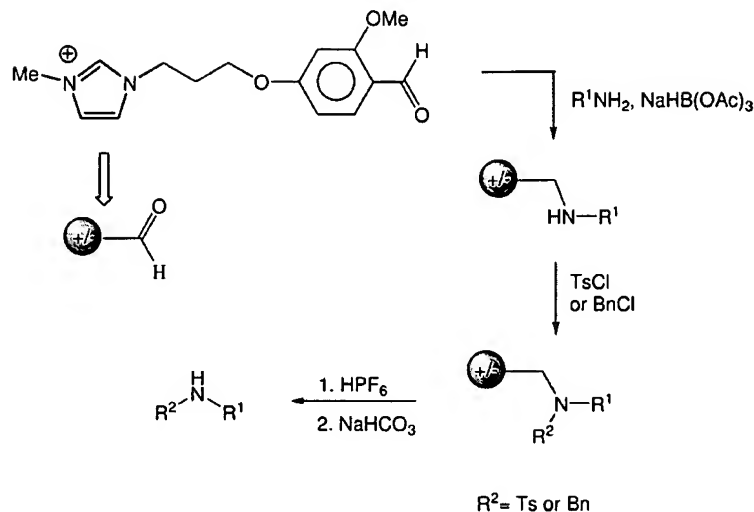


Scheme 5.5-33

The reaction of supported acrylic esters as 0.85 M solutions in an ionic liquid solvent such as *n*-butyltrimethylammonium or ethylmethyimidazolium triflimide ([*bu*Me<sub>3</sub>N][NTf<sub>2</sub>] or [EMIM][NTf<sub>2</sub>]) with an excess of cyclopentadiene at room temperature goes to completion within 2 h. After removal of the excess diene by washing with ether, the cycloadducts are cleaved from the support by transesterification in boiling methanol in the presence of traces of HCl. Extraction with ether or bulb to bulb distillation under vacuum allows the isolation of the methyl esters of the adducts in excellent yields (80–90%) and purities (Scheme 5.5-32). No influence of either the nature of the solvent or the supporting salts on the isolated yields of the norbornene derivatives or the *endo/exo* selectivity was observed [11, 21].

No leaching of the supports was observed during the extraction operations and the solutions could be recycled and reused without problems. Other 1,3-dienes gave similarly good results. The productivity of the BTSILs could be increased by using the following polyfunctional supporting salts carrying 2, 3 or 4 acrylic groups (Scheme 5.5-33). Isolated yields of the adducts and the *endo/exo*-ratio after transesterification were the same.

These reactions could be easily monitored by routine NMR-spectroscopy (see Fig. 5.5-2) at the concentrations used to perform the reaction, i. e. 0.85 mol l<sup>-1</sup> and the crude reaction mixture was analyzed by capillary GC [51].



Scheme 5.5-34

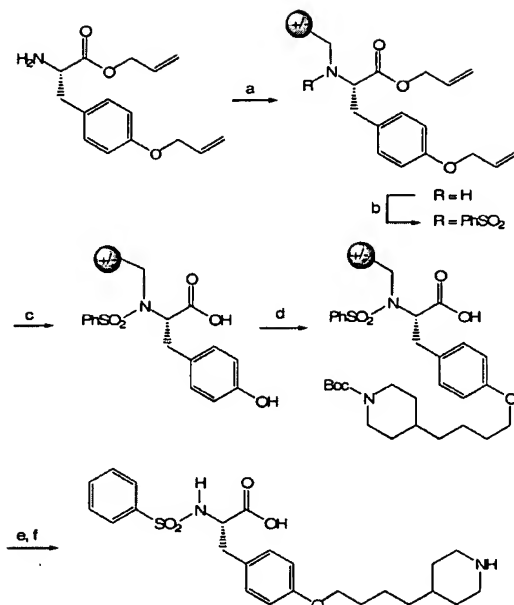
An *N*-methylimidazolium chloride-based ionic support bearing an aldehyde, analogous to the known AMEBA [52] solid support [53] readily dissolves in an ionic liquid solvent such as *n*-butylimidazolium hexafluorophosphate ([BMIM][PF<sub>6</sub>]). It has been used to prepare a set of diverse sulfonamides and amides according to (Scheme 5.5-34) [39] with isolated yields ranging from 26 to 54% and purities from 55 to 95%, as determined by NMR spectroscopy, comparable to those obtained from solid support chemistry [53]. Reactions were monitored by HPLC. No leakage of the ionically supported substrate into the aqueous or organic phase occurred.

This methodology has been applied to the multistep synthesis of a sulfonlated tyrosine derivative, a highly potent analog of the antithrombic drug tirofiban according to (Scheme 5.5-30). The target compound was obtained in 1% yield over 5 steps after purification by preparative HPLC (Scheme 5.5-35).

Multicomponent reactions are an increasingly important class of reactions because they combine simplicity, atom economy and efficiency in terms of both yields and the introduction of molecular diversity [52]. These reactions have been described on both solid and soluble supports, as well as giving an easy entry into libraries of compounds. BTSILs are appropriate soluble supports for such reactions. This is illustrated by the tetrahydroquinoline synthesis developed in solution and on solid supports [52]. The reaction of an aniline supported on an ammonium salt in solution in [buMe<sub>3</sub>N][NTf<sub>2</sub>] with benzaldehydes and electron-rich olefins such as styrene, cyclopentadiene and indene in the presence of a trace of TFA, led quantitatively and rapidly (20 to 60 min) to the corresponding tetrahydroquinolines at room temperature according to (Scheme 5.5-36) [21, 51].

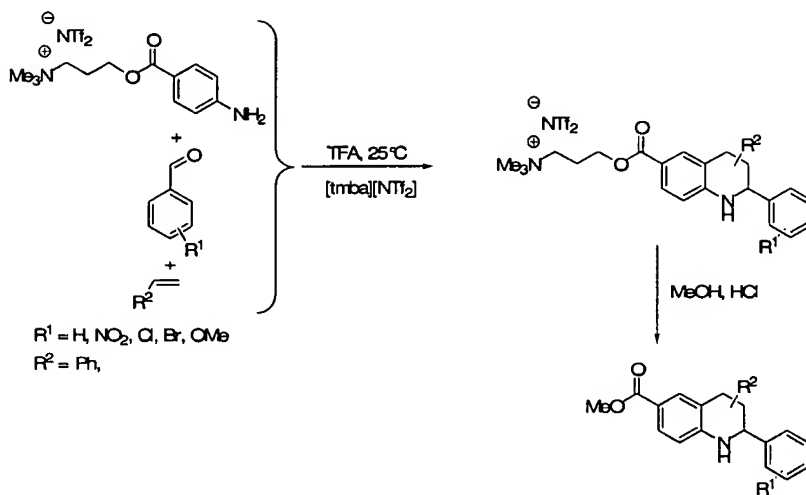
After washing the crude reaction mixture to eliminate the excess reagents and impurities, followed by transesterification, methyl esters of a series of the desired

## 512 | 5 Organic Synthesis



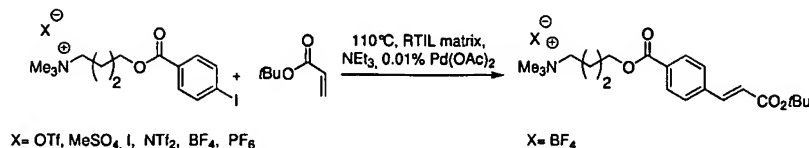
All reactions are performed in [BMIM][PF<sub>6</sub>]. (a) NaBH(OAc)<sub>3</sub>, HOAc, 16h; (b) PhSO<sub>2</sub>Cl, Et<sub>3</sub>N, 1h; (c) Pd(PPh<sub>3</sub>)<sub>4</sub>, pyrrolidine, 90°C, 45 min; (d) NaH, then N-Boc-4-(4-iodobutyl)-piperidine, 16h; (e) 2% HPF<sub>6</sub>, 10 min; (f) Et<sub>3</sub>N, then extraction with H<sub>2</sub>O.

Scheme 5.5-35



Scheme 5.5-36

## 5.5 Task-specific Ionic Liquids as New Phases for Supported Organic Synthesis | 513



Scheme 5.5-37

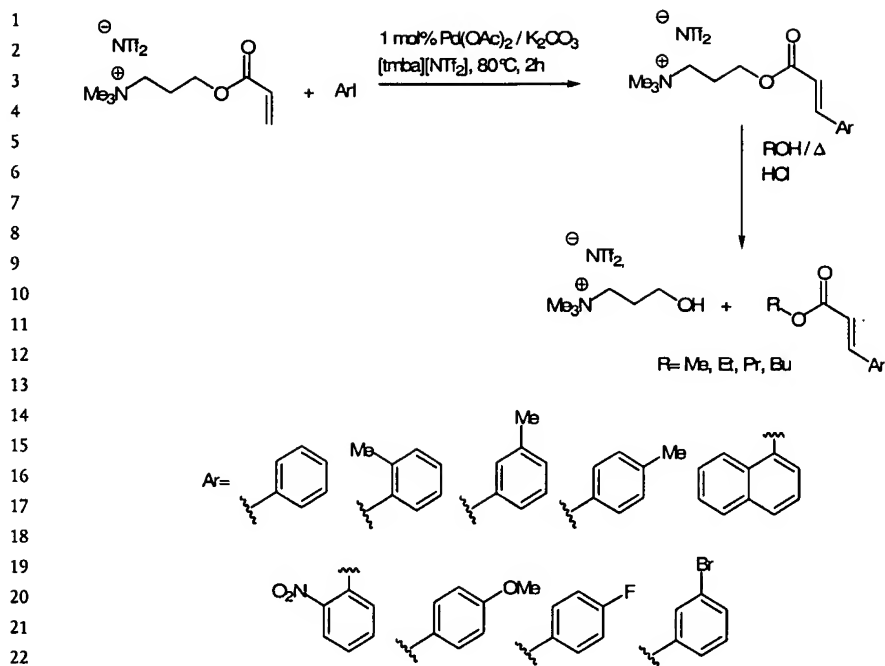
tetrahydroquinolines could be isolated in yields ranging from 65 to 90% with excellent purity.

Ionic liquids have been used extensively to perform transition metal catalyzed reactions [56]. Among these, Heck, Suzuki-Miyaura and Sonogashira C–C coupling reactions are among the most synthetically useful ones and have been studied in detail in RTILs. Supporting one of the components of the reaction on a BTSIL is an idea which comes immediately to mind. The catalyst itself can be supported via supported ligands but this will not be addressed in this chapter. All other components have been supported on BTSILs. The interest in this methodology resides in the possibility of washing out excess reagents and by-products resulting from side reactions such as reduction, not linked to the support, or the possibility of performing parallel synthesis or any other combinatorial technique.

Heck coupling has been studied in detail [18, 21]. It has been shown that, for any given catalyst, every parameter of the reaction, such as the nature of the base, of the solvent (cation and anion), of the supporting TSOS (cation and anion) and temperature has its own influence on the reaction. The solvent effect is best illustrated with the reaction of a supported 4-iodobenzoic ester on trimethylammonium tetrafluoroborate TSOS at 110 °C in the presence of 100 ppm of Pd(OAc)<sub>2</sub> solubilized in different RTILs as solvents, as illustrated in (Scheme 5.5-37). [BMIM][NTf<sub>2</sub>], [BMIM][PF<sub>6</sub>], [BMIM][BF<sub>4</sub>], [BMIM][OTf], [buMe<sub>3</sub>N][NTf<sub>2</sub>] and [(OH)PMe<sub>3</sub>N][NTf<sub>2</sub>] have been used as solvent. Conversions were monitored by HPLC. Under these conditions, no reaction was observed in imidazolium matrices but conversions were complete in trimethylammonium ILs. The anion of the supporting salt is also important. After 2 h of reaction under the mentioned conditions in [buMe<sub>3</sub>N][NTf<sub>2</sub>] as a solvent, 100% conversion was observed with [BF<sub>4</sub>]<sup>−</sup>, [PF<sub>6</sub>]<sup>−</sup>, [NTf<sub>2</sub>]<sup>−</sup> and [OTf]<sup>−</sup> whereas 33 and 69% conversions were observed for I<sup>−</sup> and [CH<sub>3</sub>SO<sub>4</sub>]<sup>−</sup>, respectively. It is worth noting that with methyl sulfate, a cheap anion, the reaction goes to completion after 5 h. This methodology has been applied to the parallel synthesis of a small library of 9 supported cinnamic esters in a [buMe<sub>3</sub>N][NTf<sub>2</sub>] solvent according to (Scheme 5.5-38). Reactions were monitored by NMR spectroscopy and were completed within 2 h. The *E*-configured olefins were obtained exclusively.

Mixing these 9 cinnamic esters and performing the transesterification with MeOH, EtOH, PrOH and BuOH led to 4 libraries of 9 different esters. The GC trace of the methyl ester library showed an excellent state of purity of the crude reaction mixture and therefore the efficiency of the methodology [21].

## 514 | 5 Organic Synthesis



Scheme 5.5-38

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Suzuki-Miyaura coupling, involving the reaction of aryl boronic derivatives with aryl halides in the presence of a palladium catalyst, is a very powerful method for the preparation of biaryls. Solutions of aryl bromides or iodides supported on onium salts via an ester link in an RTIL lead to BTSILs that can be engaged in the Suzuki-Miyaura coupling reaction with aryl boronic derivatives. Like the Heck reaction, this coupling is also sensitive to the variations in different parameters. The possibility to synthesize libraries of biaryl derivatives by parallel synthesis is illustrated by (Scheme 5.5-39) [51].

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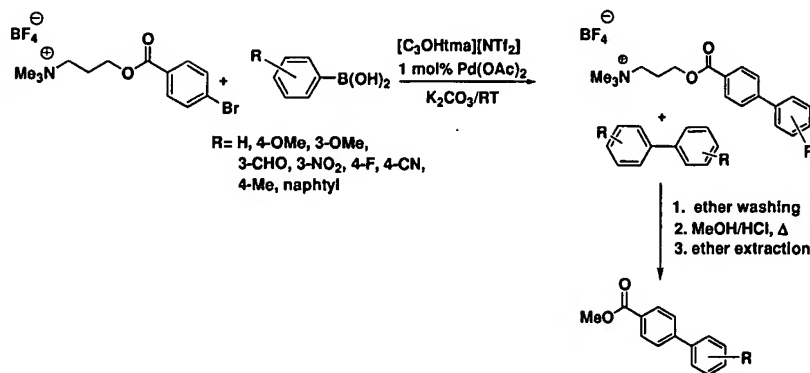
The coupling reactions went to completion within 12 h at room temperature in the 3-hydroxypropyltrimethylammonium triflimide ( $[(\text{OH})\text{PMe}_3\text{N}][\text{NTf}_2]$ ) used as the solvent in the presence of powdered potassium carbonate base. Under these conditions, 1% or less homocoupling occurred. The corresponding symmetrical biphenyl was washed out before transesterification with methanol had been conducted, which gave the biphenyl esters in yields ranging from 90 to 95% and in excellent purities.

## 5.5.3.3 Reactions of Functionalized TSOSs in Molecular Solvents

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The interest in using solutions of TSOSs in RTILs (i.e., BTSILs) as reaction media for supported organic chemistry has been reported above. These TSOSs are





Scheme 5.5-39

usually prepared in molecular solvents such as dichloromethane, DMF, acetonitrile, to mention just a few. Recently, many chemical transformations of onium salts have been reported in solution in these solvents, although the authors claim that it is ionic liquid supported organic synthesis it would be more accurate to use the expression "task-specific onium salt supported organic synthesis" or "TSOS supported organic synthesis". This idea that TSOSs can be used as soluble supports for organic synthesis in molecular solvents has been patented [21]. Indeed, the use of solutions of TSILs or TSOSs in molecular solvents offers a wide and complementary broadening of the use of BTSILs.

Coupling reactions are an excellent field for testing new soluble supports. For example, a small library of stilbenes was easily obtained by the reaction of a supported styrene on a functionalized trimethylammonium tetrafluoroborate with a mixture of 7 aryl iodides in DMF at 100 °C for 2 h. The reaction was monitored by HPLC and, after completion, the DMF was evaporated under vacuum and the residue washed several times with ether and water. Transesterification of this mixture with acidic methanol led, after evaporation and extraction with ether, to a library of 7 stilbenes in an excellent state of purity as determined by GC/MS. No impurity and particularly no starting styrene could be detected, showing that the reaction was complete (Scheme 5.5-40) [21, 51].

DMF has also been used as a solvent for Suzuki-Miyaura coupling. A supported 4-bromobenzoic ester in the presence of potassium carbonate was reacted with an array of aryl boronic acids in parallel. After 5 h at 80 °C, the reaction mixture was filtered, DMF evaporated and the products washed with ether, recrystallized and collected by filtration (Scheme 5.5-41) [51].

The results are displayed in Table 5.5-7 and show the efficiency of these systems.

Chan et al. illustrated the use of imidazolium tetrafluoroborates functionalized with 3- and 4-iodobenzoic esters in Suzuki-Miyaura cross-coupling reactions [57]. These esters were prepared by esterification of 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate in a mixture of acetonitrile and dichloromethane

## 516 | 5 Organic Synthesis

Table 5.5-7 Suzuki-Miyaura coupling in DMF


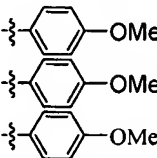
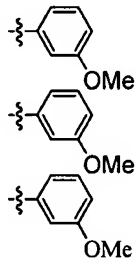
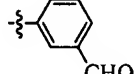
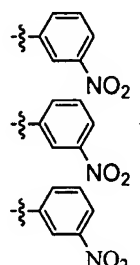
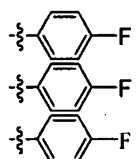
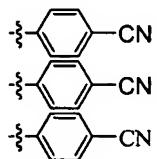
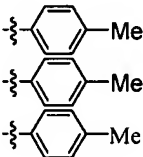
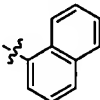
Entry	X	R	Yield (%) <sup>[a]</sup>	mp (°C)
1	[BF <sub>4</sub> ] <sup>-</sup>		87	204–206
2	[BF <sub>4</sub> ] <sup>-</sup>		82	212–214
3	[NTf <sub>2</sub> ] <sup>-</sup>		73	nd <sup>[b]</sup>
4	[NTf <sub>2</sub> ] <sup>-</sup>		65	138–140
5	[BF <sub>4</sub> ] <sup>-</sup>		75	146–148
6	[BF <sub>4</sub> ] <sup>-</sup>		82	132–134
7	[BF <sub>4</sub> ] <sup>-</sup>		70	164–166

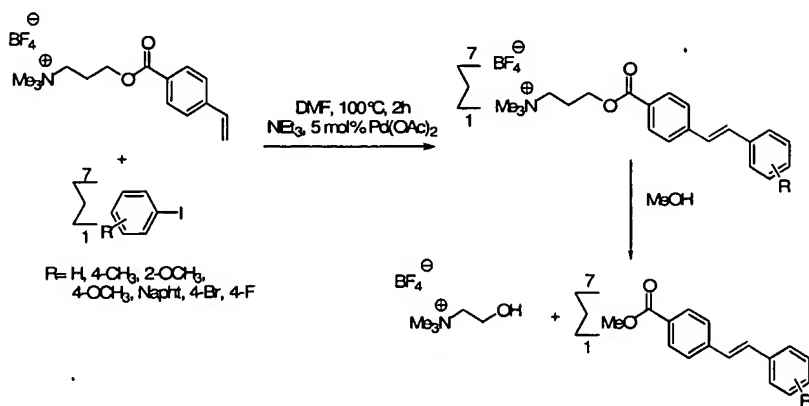
Table 5.5-7 Continued

Entry	X	R	Yield (%)	mp (°C)
8	[BF <sub>4</sub> ] <sup>−</sup>		82	198–200
9	[BF <sub>4</sub> ] <sup>−</sup>		73	oil

<sup>a</sup>Yields are for isolated pure recrystallised compounds.<sup>b</sup>nd: not determined.

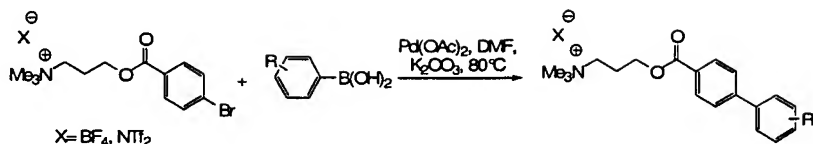
and were obtained, after the usual work-up, as solids melting at 113–115 °C for the 4-iodo and 76–79 °C for the 3-iodo derivatives (Scheme 5.5-42) [57].

Then, these iodobenzoates were submitted to Suzuki-Miyaura coupling with aryl boronic acids in water as the solvent in the presence of palladium acetate as the catalyst and cesium fluoride as the base. Some homocoupling products were washed out before cleavage by transesterification, extraction and purification of the biaryl products, which were obtained in yields ranging from 55 to 83% for the two steps. This methodology allows for the isolation of the intermediate supported biaryls as salts in a very good state of purity by simple evaporation of water followed by ether washing, which removed the excess of the starting boronic acid and the homocoupling product, leaving behind the supported coupled products.

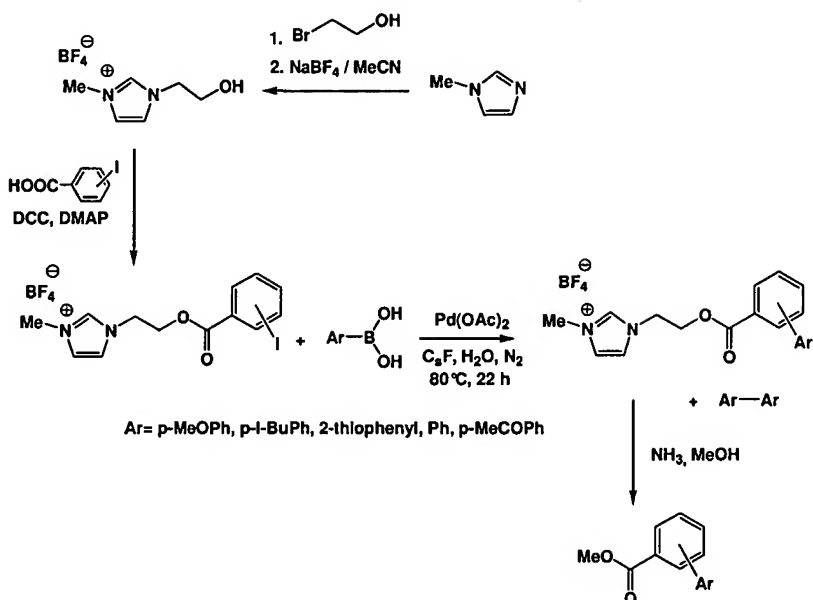


Scheme 5.5-40

## 518 | 5 Organic Synthesis



Scheme 5.5-41



Scheme 5.5-42


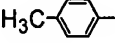

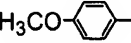
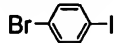

The Sonogashira coupling reaction also illustrates the possibilities of this methodology. A small library of six supported aryl acetylenes was obtained according to (Scheme 5.5-38). The supported propionic acid on the triethylammonium trifluoroborate was esterified in MeCN in 90% yield. Coupling was realized in a parallel manner in MeCN, leading quantitatively to the aryl acetylenes in 20 min at room temperature (Scheme 5.5-43). The results are summarized in Table 5.5-8 [21, 51].

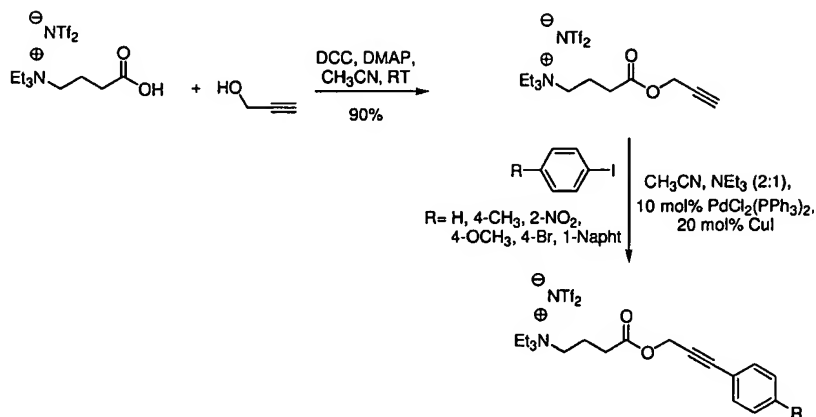
This kind of methodology has also been used for the preparation of thioureas (Scheme 5.5-44) [30].

,4-addition of primary amines on supported acrylic esters has been performed in acetonitrile followed by the reaction of the secondary amines obtained with isothiocyanates to yield thioureas. Isolation of these compounds only requires solvent evaporation, washing with ether and drying under vacuum. Good yields were obtained.

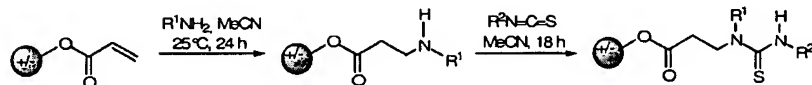
Isothiocyanato esters appended to (polyethylene glycol)-ionic liquid phases have been prepared by nucleophilic substitution with potassium thiocyanate in refluxing

Table 5.5-8 Sonogashira coupling in CH<sub>3</sub>CN at RT

Entry	Aryl iodide	Yield (%) <sup>a</sup>
1		77
2		89
3		81
4		92
5		80
6		86

<sup>a</sup>Yields refer to isolated pure products.

Scheme 5.5-43

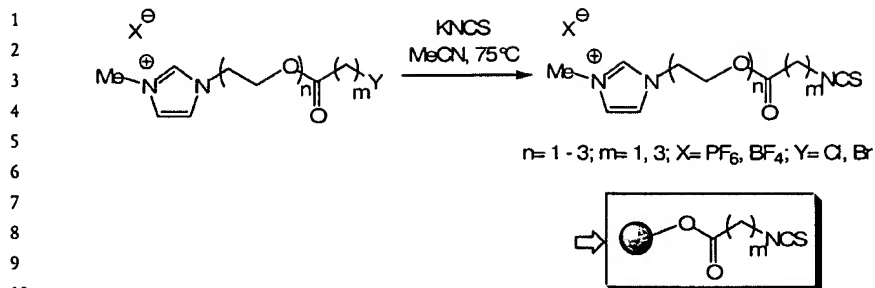


Scheme 5.5-44

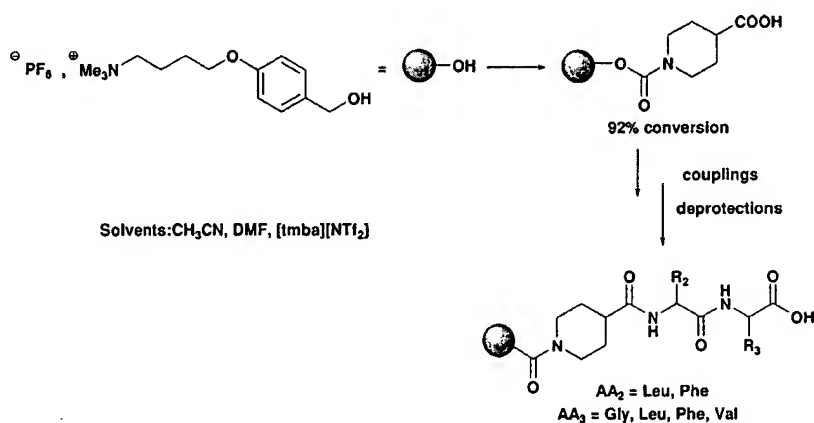
anhydrous MeCN and isolated in very good yields after elimination of the solvent under vacuum, washing and further drying under vacuum (Scheme 5.5-45) [50].

Strategies for the synthesis of peptides supported on TSOS in both directions (C to N and N to C), and convergent as well, have been demonstrated [50]. Reverse peptide

## 520 | 5 Organic Synthesis



Scheme 5.5-45

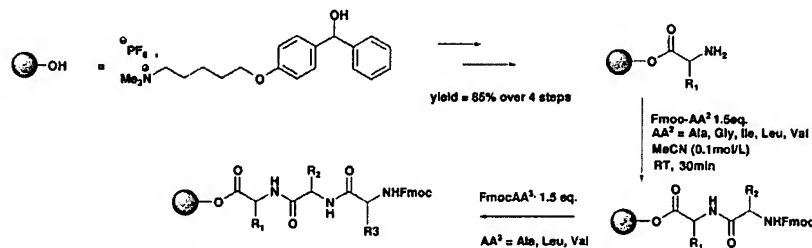


Scheme 5.5-46

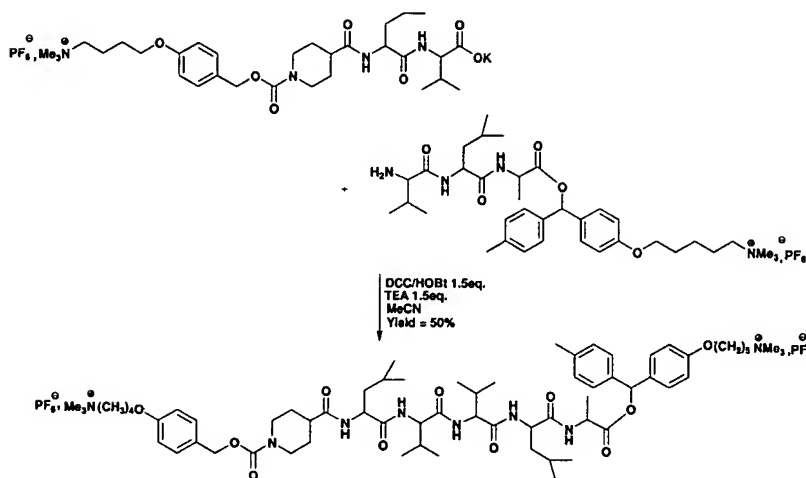
31 synthesis to obtain C-terminally modified peptides has been validated by using a  
32 TSOS derived from a Wang-type linker. The first aminoacid, isonipecotic acid, was  
33 anchored via a mixed carbonate derived from p-nitrophenyl chloroformate (92%).  
34 The following step is a peptide coupling, which can be done using HOBt/DCC  
35 (or DIC) as reagents and only 1.5 equivalents of amino acid. The conversion is  
36 quantitative when the matrix is MeCN or  $[buMe_3N][NTf_2]$ . Gly-OMe, Ala-OMe,  
37 Val-OMe, Leu-OMe, Phe-OMe were coupled as second aminoacids with yields of  
38 isolated supported peptides in the range of 85%. Methyl ester function is saponified  
39 with  $Me_3SiOK$  and completed within 2 h. A second peptidic coupling with either  
40 Gly-OMe, Leu-OMe, Phe-OMe or Val-OMe is realized to give supported tripeptides.  
41 It is then possible to cleave the peptides from the support with TFA or TMSBr  
42 (Scheme 5.5-46).

43 Direct peptide synthesis supported on TSOS has also been developed using a  
44 Fmoc strategy with a linker functionalized by a benzhydryl alcohol. Grafting of  
45 the first aminoacid is followed by a metathesis of the chloride or bromide anion

## 5.5 Task-specific Ionic Liquids as New Phases for Supported Organic Synthesis | 521



Scheme 5.5-47

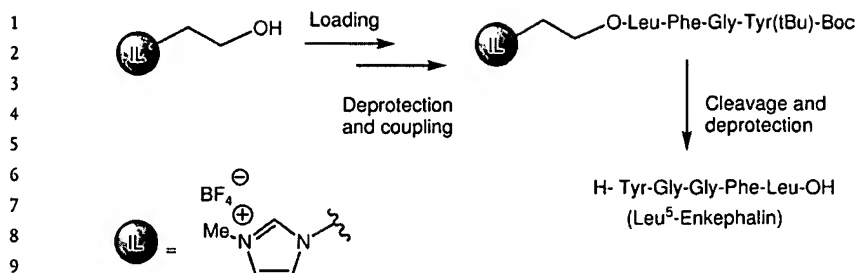


Scheme 5.5-48

to hexafluorophosphate and Fmoc deprotection. The supported aminoacids are isolated with an 85% yield over four steps. Ala, Phe, Gly, Ile, Leu and Val have been supported in this manner. A second aminoacid i.e. Fmoc-Ala, Fmoc-Gly, Fmoc-Ile, Fmoc-Leu and Fmoc-Val, is coupled following the same procedure and work-up. Either HBTU or DCC/HOBt can be used as coupling reagents. After Fmoc deprotection, the supported pure dipeptides are isolated with yields of around 85%. Further coupling under the same conditions leads to supported tripeptides with good yields. These peptides can be cleaved easily from the ionic support (Scheme 5.5-47).

Finally, convergent peptide synthesis under homogeneous conditions has been demonstrated: two supported peptides prepared by inverse and direct peptide synthesis have been successfully coupled to obtain a supported hexapeptide as a bis-ammonium salt (Scheme 5.5-48) [50].

## 522 | 5 Organic Synthesis



Scheme 5.5-49

The synthesis of a bioactive pentapeptide, Leu<sup>5</sup>-enkephalin, in good yield and reasonable purity was developed on functionalized imidazolium salts in a MeCN/CH<sub>2</sub>Cl<sub>2</sub> solvent mixture (Scheme 5.5-49) [59].

This approach, named ILSPS for ionic liquid supported peptide synthesis, offers potential advantages as well as limitations in comparison to the existing methods of peptide synthesis. One important advantage is that, at each step, the intermediate can be purified easily by solvent washings. High loading is an important feature of these supports due to their low molecular weight. This is interesting for large-scale preparation, as is their low cost. Furthermore, the structure and purity of each intermediate can be verified by routine spectroscopic methods and HPLC.

#### 5.5.3.4 Lab on a Chip System Using a TSIL as a Soluble Support

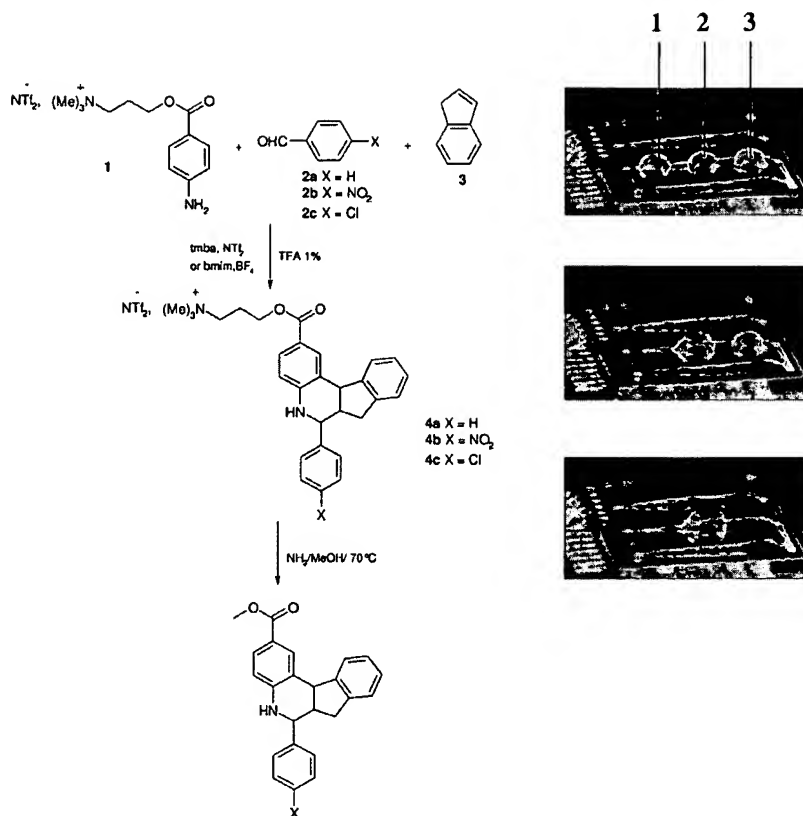
A powerful tool to synthesize easily minute amounts of organic compounds on demand by using both ionic liquids droplets as microreactors and electrowetting as a fluidic motor has been described. These droplets can be moved, divided and combined on an open digital microfluidic lab-on-a-chip system [60]. This has been demonstrated with BTSILs used as reaction media and supports, properly functionalized to perform the Grieco's multicomponent synthesis of tetrahydroquinolines (Fig. 5.5-3). It is assumed that this original concept should impact many areas, notably combinatorial chemistry, parallel synthesis, optimization of protocols, synthesis of dangerous products and embedded chemistry in a portable device.

#### 5.5.4

#### Conclusion

Although the chemistry of TSILs, BTSILs and TSOSs is still in its infancy, it can be safely stated that, generally speaking, they should have a bright future. Almost any functionalization of these salts is possible, therefore opening the way to task-specific materials and molecules. Numerous developments are predictable, not only in this area of supported chemistry, but in several other fields of chemistry including combinatorial chemistry, physical organic chemistry, microreactors and material sciences. It clearly appears from this review that TSILs, BTSILs and TSOSs are a





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**Fig 5.5-3** Schematic representation of Grieco's reaction in a droplet microreactor. Photographs of droplet displacement during the Grieco's reaction are shown on the right of this figure. The droplet containing **1** was allowed to converge towards the droplet containing **2** and TFA. After mixing, the obtained droplet was directed towards the droplet containing **3**, thus leading quantitatively to adducts **4** which could be cleaved to the corresponding methyl esters by transesterification.

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valuable addition to the arsenal of tools available for supported chemistry and in particular in the field of solution phase chemistry. Several advantages of these new supports have been pointed out in this chapter including simple synthesis, solution phase reaction conditions, flexibility, diversity of feasible chemistry, stability, high loading, easy monitoring of reactions, to mention but a few. Problems arise from availability from commercial sources, viscosity, chemical stability which depends very much on both the cations and the anions to be used, and sensitivity to moisture which requires special precautions. No doubt solutions will be found to all these problems.

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## 5.6

## Supported Ionic Liquid Phase Catalysts

Anders Riisager and Rasmus Fehrmann

## 5.6.1

## Introduction

An important concept in catalysis which attracts increasing attention involves the transformation of homogeneous catalytic reactions into heterogeneous processes where the catalyst can be easily separated from the reaction mixture, allowing reuse and continuous flow operation [1]. In the literature several general reviews have dealt with the subject [2–5] along with special surveys focusing on issues such as multiphase catalytic approaches [6–10], organometallic catalysis [11], enantioselective catalysis [12], oxidation catalysis [13], and Lewis acid catalysis [14, 15].

In Section 5.3 it was demonstrated with many examples that ionic liquids are indeed a very attractive class of solvents for catalysis in liquid–liquid biphasic operation (for some selected reviews see Refs. [16–20]). In this section, we will focus on a different way to apply ionic liquids in catalysis, namely the use of an ionic liquid catalyst phase supported on a solid carrier, a technology that has become known as “supported ionic liquid phase (SILP)” catalysis. In comparison to the conventional liquid–liquid biphasic catalysis in ionic liquid–organic liquid mixtures, the concept of SILP-catalysis combines well-defined catalyst complexes, nonvolatile ionic liquids, and porous solid supports in a manner that offers a very efficient use of the ionic liquid catalyst phase, since it is dispersed as a thin film on the surface of the high-area support. Recently, the initial applications using such supported ionic liquid catalysts have been briefly summarized [21]. In contrast to this report, where the applications were distinguished by the choice of support material, the compilation here will divide the applications using the supported ionic liquid catalysts into sections according to the nature of the interaction between the ionic liquid catalyst phase and the support.

## 5.6.2

## Supported Ionic Liquid Phase Catalysts

## 5.6.2.1 Supported Catalysts Containing Ionic Media

The idea to immobilize catalytically active salts or salt solutions on a support to obtain a solid heterogeneous-like catalyst system, maintaining the selectivity and

1 efficiency of the homogeneous catalyst, is far from new. The principle of the concept  
2 was already noted in 1968 [22] and has, for example, later been realized for organic  
3 reactions using the methodology of gas-liquid phase-transfer catalysis (GL-PTC)  
4 [23]. In GL-PTC; organic reactions are conducted by a continuous-flow procedure  
5 in which the organic, gaseous reactants are converted by passing the gas through  
6 a liquid phase-transfer catalyst supported on a porous, solid material (typically  
7 organic polymers or inorganic oxides with low surface acidity). Usually, the liquid  
8 phase-transfer catalyst is composed of relatively stable and non-volatile, low melting  
9 tetraalkyl phosphonium salts (e.g. [Bu<sub>4</sub>P]Br with a melting point of 103 °C) with  
10 or without the presence of additional co-catalysts, providing activation of anions to  
11 carry out reactions such as halogen exchange, forming alkyl halides from alcohols,  
12 transesterification and isomerization [24, 25].

13 In a more fundamental perspective the concept of confining catalytically active  
14 salts on supports may be regarded as a branch of the common concept of supported  
15 liquid phase (SLP) catalysts, where a non- or low-volatile catalyst solution of, for  
16 example, pyrosulfates [26], hydrophilic polymer glycols [27–29], phthalates [22] or  
17 water (i.e. supported aqueous phase, SAP) [30–33] are deposited on a high-surface  
18 area porous support.

19 In the literature terms such as supported molten salt (SMS) catalysts, supported  
20 ionic liquid catalysts (SILC) and supported ionic liquid-phase (SILP) catalysts, have  
21 been used somewhat indiscriminately to describe catalyst systems containing a  
22 catalytic ionic phase. In this section we will use the terms “molten salt” or “ionic  
23 liquid” to indicate the melting point of the fluid phase in the systems. Furthermore,  
24 we will distinguish between the terms “SILC” and “SILP.” “SILP” is used when  
25 the ionic liquid is performing mainly as an immobilizing solvent for the catalytic  
26 components. “SILC” is used in cases where the ionic liquid itself, ionic liquid ions  
27 or ionic liquid-like fragments are behaving as the catalytic species.

#### 29 5.6.2.1.1 Process and engineering aspects of supported ionic liquid catalysts

30 During catalytic reactions using supported ionic liquid-type catalysts gaseous or  
31 vapor-phase reactants diffuse through the residual pore space of the catalyst, dissolve  
32 in the liquid catalyst phase, and react at catalyst sites within the thin liquid catalyst  
33 film dispersed on the walls of the pores in the support material, as illustrated in  
34 Fig. 5.6-1. The products then diffuse back out of the catalyst phase into the void  
35 pore space and further out of the catalyst particle.

36 In general, the catalytic performance of SLP-type catalysts depends considerably  
37 on the amount of the liquid solvent in the supported catalyst, that is liquid loading  
38 ( $\alpha$ , defined as the ratio between the liquid volume and support pore volume). Thus,  
39 on the one hand the amount of liquid must be large enough to constitute a thin film  
40 on the solid, while on the other hand, still low enough to avoid pore plugging that  
41 would restrict the diffusion of the reactants. As a consequence, the catalyst layer  
42 is often 20 Å or less, corresponding to a diffusion layer of only a few molecules  
43 thick. This makes diffusion problems (which are regularly found for reactions in  
44 bulk liquids, and especially with the relatively viscous ionic liquids) very unlikely.  
45 In addition, the distribution of the liquid inside the porous support is also of

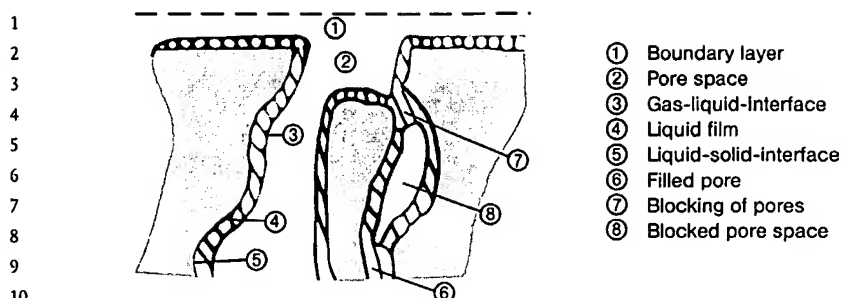


Fig. 5.6-1 The principle of a supported liquid phase (SLP) catalyst (from Ref. [34]).

great importance and may generally be determined by several interacting factors including, for example, pore radii distribution of the support, the capillary forces, the wetting characteristics of the liquid and possible ionic liquid–support interactions [34]. Moreover, percolation theory may be used to model the liquid distribution in SLP catalysts [35]. More details of the behavior and catalytic performance of SLP-type catalysts with respect to liquid distribution and diffusion can be found in the literature (e.g. Refs. [22, 26, 36–40]).

The concept of using supported ionic liquid catalysts combines the most attractive features of homogeneous catalysis such as the uniform nature of the catalytic centers, high specificity and selectivity of the catalyst, with the most attractive features of heterogeneous catalysts, such as large interfacial reaction area, ease of separation of products and catalyst, high system stability and the potential to use very simple processing such as fixed-bed reactor technology. This quite unique combination has made the methodology very attractive for many applications, as will be illustrated in the following sections.

It should, however, be pointed out that the SILP and SILC techniques are only straightforward to apply for continuous gas-phase reactions, where the advantage of using a liquid with very low vapor pressure can be fully exploited. In contrast, the application of the technology in liquid-phase reactions may be very restricted, since even a minor solubility of the ionic liquid in the feedstock/product mixture will remove the catalyst from the surface (due to the very small amount of ionic liquid on the support). Even worse, the film of the immobilized catalyst phase can physically be removed from the support by mechanical forces, for example, the convective liquid flow, even in the case of complete immiscibility.

#### 5.6.2.1.2 Characteristics of ionic liquids on solid supports

In contrast to the increasing information on the bulk properties of ionic liquids, very little is known about the interfacial structure of ionic liquids with other phases. Examinations of gas–ionic liquids interfaces of 1,3-dialkylimidazolium-based liquids using direct recoil spectroscopy [41] or surface vibrational spectroscopy [42–44] have provided some general indicative information about the surface composition

1 and orientation of the imidazolium cations with respect to the interface. Here, it  
2 was found that the preferred orientation of the imidazolium cations at the interface  
3 could be either perpendicular or parallel (with some tilting and twist of the ring  
4 structure with respect to the interface) depending on factors such as water in the  
5 ionic liquid, the length of the alkyl chains in the imidazolium cations, and anion  
6 interactions. Moreover, the examinations performed with direct recoil spectroscopy  
7 suggested that the surface of the ionic liquids is ionic in nature and equally occupied  
8 by the anions and cations with no segregation [44].

9 With respect to the interfacial structure of ionic liquids with solids, the molecular  
10 layering and local order in thin liquid crystalline films of [RMIM][PF<sub>6</sub>] ionic liquids  
11 with long alkyl chains (e.g., R = dodecyl and octadecyl) on solid silicon supports  
12 have been studied using X-ray reflectivity [45]. Here, thin films of the crystalline  
13 ionic liquids with a thickness of 100–210 Å were deposited on polished and cleaned  
14 silicon wafers by initial spin-coating of a solution of the ionic liquids in methanol  
15 followed by heating the samples into the isotropic liquid state and crystallization.

16 In all cases, the initial spin-coated films showed a featureless smooth decay  
17 profile in the X-ray reflectivity data, indicating that the ionic liquid was not de-  
18 posited in a regular, ordered manner (i.e. rough films). On melting, however, thin  
19 homogeneous, isotropic liquid films were observed which, upon further cooling  
20 to crystallization, displayed sharp Bragg diffraction peaks in the reflectivity pro-  
21 files, indicative of an ordered structure. Furthermore, modeling of data obtained  
22 from an ordered film of, for example, 1-methyl-3-octadecylimidazolium hexafluorophosphate, suggested, that a layered ionic liquid structure adopted on the silicon  
23 consisted of a multilayer stack of interdigitated amphiphilic bilayers with charged  
24 layers at the silicon and air interfaces, that is, the surface of the crystalline liquid is  
25 predominately ionic in character. This result is in accordance with analogous results  
26 obtained from measurements of gas–liquid interfaces by direct recoil spectroscopy  
27 [44].

28  
29 In another study which used a support more relevant to supported ionic liquid  
30 catalysts, sum-frequency vibrational spectroscopy (SFVS) was used to study the  
31 structure of ionic liquid cations present at the interface between a silica support  
32 and imidazolium ionic liquids [RMIM][X], with R = hexyl, octyl or decyl (i.e. C<sub>6</sub>,  
33 C<sub>8</sub> or C<sub>10</sub>), and X = (CF<sub>3</sub>(CF<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>)<sub>2</sub>N with n = 0 or 1 [46]. The measurements  
34 were performed by introducing the ionic liquids in a thoroughly cleaned fused silica  
35 prism.

36 For all the examined imidazolium-based ionic liquids, the ring structure of the  
37 planar imidazolium cation (based on the HCCH-ring dipole orientation) was found  
38 to be positioned in a tilted, vertical position at an angle ( $\theta$ ) of 16 to 32° with respect to  
39 the silica surface normal (see Fig. 5.6-2). This is in contrast to the parallel orientation  
40 found in studies of similar ionic liquids at the air–ionic liquid interface [41].

41 Furthermore, the orientation of the alkyl chain (i.e. hexyl, octyl or decyl chain)  
42 on the imidazolium cation was pointing in a nearly perpendicular orientation away  
43 from the silica surface with a high degree of conformational order and few gauche  
44 defects. In Table 5.6-1 some of the structural parameters determined for the exam-  
45 ined ionic liquids are summarized.

## 530 | 5 Organic Synthesis

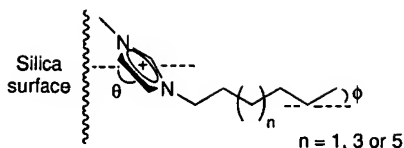


Fig. 5.6-2 Schematic illustration of the orientation of imidazolium cations at the surface of silica determined by sum-frequency vibrational spectroscopy (modified from Ref. [46]).

Table 5.6-1 Tilt angles for the terminal methyl and imidazolium ring determined from the SFVS intensity data (modified from Ref. [46])

	Alkyl-CH <sub>3</sub> tilt angle, $\phi$ (°)	Alkyl chain tilt <sup>a</sup> (°)	HCCH tilt angle, $\theta$ (°)
[C <sub>6</sub> MIM][(CF <sub>3</sub> SO <sub>2</sub> ) <sub>2</sub> N]	36 ± 4	1 ± 4	30 ± 4
[C <sub>8</sub> MIM][(CF <sub>3</sub> SO <sub>2</sub> ) <sub>2</sub> N]	38 ± 8	3 ± 8	21 ± 8
[C <sub>10</sub> MIM][(CF <sub>3</sub> SO <sub>2</sub> ) <sub>2</sub> N]	39 ± 6	4 ± 6	32 ± 5
[C <sub>6</sub> MIM][(CF <sub>3</sub> CF <sub>2</sub> SO <sub>2</sub> ) <sub>2</sub> N]	25 ± 5	10 ± 5	16 ± 6
[C <sub>8</sub> MIM][(CF <sub>3</sub> CF <sub>2</sub> SO <sub>2</sub> ) <sub>2</sub> N]	32 ± 4	3 ± 4	17 ± 5
[C <sub>10</sub> MIM][(CF <sub>3</sub> CF <sub>2</sub> SO <sub>2</sub> ) <sub>2</sub> N]	42 ± 10	7 ± 10	20 ± 4

<sup>a</sup> Assumes an all-trans chain conformation.

In addition to the interfacial structure of the imidazolium cation, the organization of water at the surface was also determined using water-equilibrated ionic liquids. Here, nearly identical ice-like and “water-like” features were observed for both the water–silica surface and the water-containing ionic liquid–silica surface. Moreover, the water molecules associated with the ionic liquids at the silica interface were hydrogen-bonded in small, structurally defined configurations with the bis(perfluoroalkylsulfonyl)imide anions, consistent with previous infrared spectroscopic studies of similar materials [47].

In summary, the few initial studies conducted so far on the interfacial structure between ionic liquids and solid surfaces clearly suggest – in a more general context – that confinement of ionic liquids on solid surfaces definitely induces some distinctive, structural control of the molecular layering of the ionic liquid and of the ionic liquid distribution (i.e. wetting ability). However, further investigations are surely needed to elucidate these effects in the context of supported ionic liquid catalysis in more detail.

#### 5.6.2.2 Early Work on Supported Molten Salt and Ionic Liquid Catalyst Systems

##### 5.6.2.2.1 High-temperature supported molten salt catalysts

Development and applications of supported ionic salt catalyst systems can generally be divided into periods, which are closely related to the liquid temperature range of the ionic salts used (Fig. 5.6-3). Since low-melting ionic liquids have only been prepared relatively recently, most applications using these supported molten salt



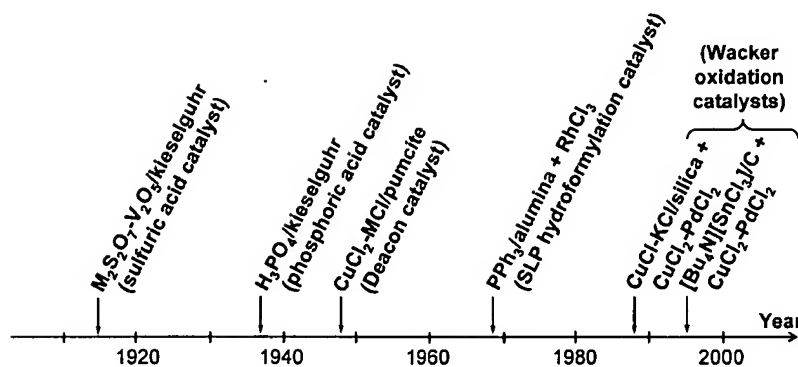


Fig. 5.6-3 Development of supported ionic salt catalyst systems.

catalysts have been restricted to temperatures higher than 200 °C and hence to catalyst systems which are stable at these temperatures.

The first supported molten salt catalyst systems date from 1914, where BASF filed a patent on a silica-supported  $V_2O_5$ -alkali pyrosulfate sulfur dioxide oxidation catalyst [48], which even today – as a slightly modified catalyst system – is still the preferred catalyst for sulfuric acid production [49]. However, it took many years to realize in the 1940s [50, 51], that the catalyst system actually was a molten salt SLP-type catalyst system which is best described by a mixture of vanadium alkali sulfate/hydrogensulfate/pyrosulfate complexes at reaction conditions in the temperature range 400–600 °C with the vanadium complexes playing a key role in the catalytic reaction [49].

In the period from the late 1930s to the late 1970s several other molten salt catalyst systems (mostly with salts melting in the range 200–500 °C) have been prepared and applied for various organic reactions, for example, condensations, cracking reactions, isomerizations, halogenations and oxidations (for more details see Ref. [52] and references cited therein). In many cases these supported molten salt catalysts proved to be highly reactive but also quite corrosive catalyst phases. Some of the most important supported catalyst systems developed during this period include the industrial Deacon catalyst [26] and the related oxychlorination catalyst systems [52] used for the oxidation of hydrogen chloride and the oxidative chlorination of unsaturated hydrocarbons (e.g. ethylene), respectively. Generally the catalysts are composed of a supported molten salt mixture of  $CuCl_2$ – $CuCl$ /alkali metal chlorides/rare earth chlorides often promoted with other transition metal chlorides (e.g.  $ZnCl_2$  and  $FeCl_3$ ) for the oxychlorination reactions. Also the solid silica- or kieselguhr-supported phosphoric acid catalyst used for petrochemical reactions such as, for example, olefin oligomerization and alkylations, was developed during these years after their initial invention in the 1930s [26]. In 1970, systems of supported copper oxide and mixed  $CuO$ /M-oxide ( $M = Cr, Co, Mn$  or  $V$ ) was reported as hydrocarbon oxidation catalysts [53]. The systems were generated by

## 532 | 5 Organic Synthesis

1 thermal treatment of a eutectic mixture of alkali metal salts containing copper  
2 salts (e.g.  $\text{CuSO}_4\text{--NaHSO}_4\text{--KHSO}_4$ , melting point  $<160\text{ }^\circ\text{C}$ ), on high-surface area  
3 alumina or silica. Noticeably, only the calcinated catalysts were applied for oxida-  
4 tion reactions and not the supported liquid salt pre-catalysts themselves. A few  
5 years later, however, the use of analogous supported eutectic salt catalyst systems  
6 containing alkali metal halides and transition metal halides such as, for example,  
7  $\text{KCl--LiCl--MnCl}_2$  supported on alumina, were applied by Monsanto [54] for the  
8 formation of  $\text{C}_2\text{--C}_4$  alkenes by gas-phase dehydrogenation of the corresponding  
9 alkanes at temperatures above the temperature of fusion of the eutectics of the  
10 systems.

11  
12  
13 5.6.2.2.2 Low-temperature supported catalysts

14 An early and possibly the first example of a supported catalyst system consisting of  
15 a relatively low-melting salt comprising a transition metal species was reported for  
16 aerial partial oxidation of ethylene to acetaldehyde (Wacker oxidation) [55]. The cat-  
17 alyst contained  $\text{CuCl}_2\text{--PdCl}_2$  dissolved in an eutectic  $\text{CuCl/KCl}$  melt (65:35 mol%)  
18 on a porous silica gel support, and proved stable during 150 h continuous reaction  
19 ( $195\text{ }^\circ\text{C}$ , 16 bar), providing a product selectivity for acetaldehyde of 95%. In contrast,  
20 an analogous water–ethylene glycol (50:50 vol.%) catalyst system deactivated fast  
21 during reaction due to evaporation of the volatile liquid solvent, clearly indicating  
22 the importance of using a low-volatile reaction medium for the continuous process.  
23 Hence, although the melting point of the supported molten salt (melting point  
24  $150\text{ }^\circ\text{C}$ ) was higher than defined for an ionic liquid, the potential of such supported  
25 catalyst systems was clearly documented at this early stage.

26 In a later work, both the  $\text{CuCl/KCl}$  molten salt Wacker oxidation system and  
27 a  $[\text{Bu}_4\text{N}][\text{SnCl}_3]$  system (melting point  $60\text{ }^\circ\text{C}$ ) was applied to the electrocatalytic  
28 generation of acetaldehyde from ethanol by co-generation of electricity in a fuel  
29 cell [56]. In the cell set-up, porous carbon electrodes supported with an ionic liquid  
30 catalyst electrolyte were separated by a proton conducting membrane (Fig. 5.6-4),  
31 and current efficiency and product selectivity up to 87% and 83%, respectively, were  
32 reported at  $90\text{ }^\circ\text{C}$ .

33 In addition to the Wacker oxidation catalysts, supported eutectic molten salt  
34  $\text{CuCl/KCl}$ -based catalyst systems have also been examined for other processes in-  
35 cluding, for example, production of synthesis gas from methanol for the use as  
36 on-board hydrogen production in vehicles [57] and quantitative combustion of chlo-  
37 rinated hydrocarbons to  $\text{CO}_x$  and  $\text{HCl/Cl}_2$  at ambient pressure ( $200\text{--}500\text{ }^\circ\text{C}$ ) with  
38 silica-based systems [58, 59].

39 Silica-supported catalyst systems comprised of tetra-n-butylammonium chloride  
40 and  $\text{PdCl}_2$  with  $\text{CoCl}_2/\text{CuCl}_2$  promoters (melting points ca.  $60\text{ }^\circ\text{C}$ ) have also been  
41 used for hydrodechlorination of chloroform with hydrogen at  $90\text{--}150\text{ }^\circ\text{C}$  [60]. As  
42 one reason for the observed catalyst deactivation the authors propose the thermal  
43 ionic liquid decomposition ( $[\text{Bu}_4\text{N}]\text{Cl}$ ,  $T_d = 170\text{ }^\circ\text{C}$ ), which seems very likely since  
44 tetraalkyl ammonium salts are known to undergo dealkylation under the applied  
45 conditions [61, 62].

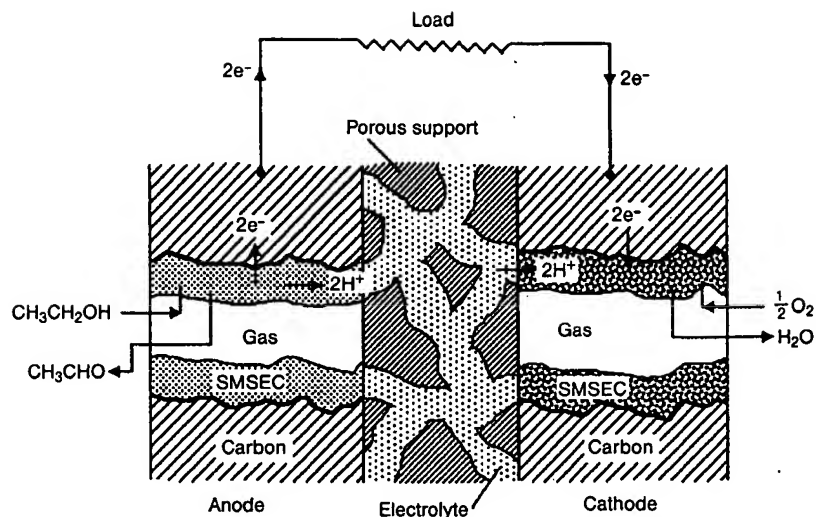


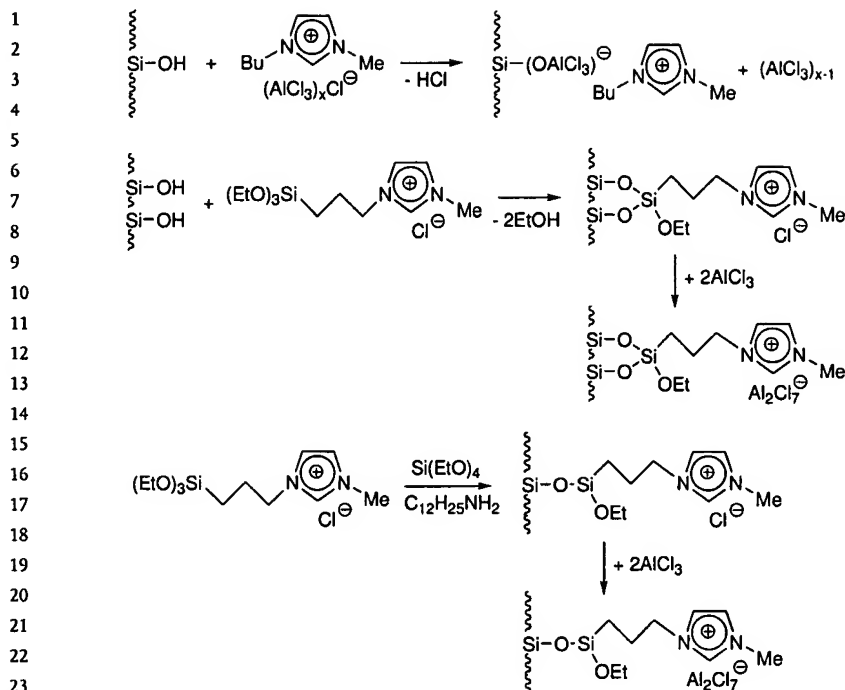
Fig. 5.6-4 Schematic illustration of a supported ionic liquid fuel cell containing the Wacker oxidation system (SMSEC: supported molten salt electro-catalyst) for co-generation of acetaldehyde and electricity from ethanol (from Ref. [56]).

### 5.6.2.3 Ionic Liquid Catalysts Supported through Covalent Anchoring

#### 5.6.2.3.1 Supported Lewis acidic chlorometalate catalysts

Supported Lewis acidic ionic liquid catalysts were first introduced for selective low-temperature alkylations of olefins to generate hydrocarbon fuels in two-phase systems [63–65]. Later, related systems were developed for Friedel-Crafts alkylations in liquid- and gas-phase reactions [66, 67] and for gas-phase disproportionation of  $C_5$ -feedstocks [68]. Generally, the catalysts were prepared by confining pre-formed, catalytically active ionic liquids on supports (e.g. silica) by impregnation. In a typical Friedel-Crafts catalyst preparation a previously dried support was treated with a chloroaluminate ionic liquid until its appearance changed from dry to wet powder [69, 70]. Then the mixture was stirred for an extended period of time before the excess ionic liquid was removed via Soxhlet extraction and vacuum dried. Mostly 1,3-dialkylimidazolium or pyridinium chloroaluminate ionic liquids were used, which induced reactions between the chloroaluminate anions and the support surface OH-groups, resulting in covalent anchoring of anions to the support accompanied by HCl liberation ((Scheme 5.6-1), top) [67, 69]. In principle, this method allows the cation to be widely varied, while the anion should have a high affinity for oxygen to remain surface bonded. Otherwise, leaching can be expected in liquid phase reactions, as has been demonstrated in acylation reactions using analogous silica- and charcoal-supported SILC materials containing less Lewis acidic and less oxophilic chloroferrate anion [71].

## 534 | 5 Organic Synthesis



**Scheme 5.6-1** Preparation of supported Lewis acidic chloroaluminate ionic liquids catalysts by impregnation with [BMIM][ $(\text{AlCl}_3)_x\text{Cl}$ ] (top), by grafting of 1-(triethoxysilylpropyl)-3-methyl-imidazolium chloride followed by  $\text{AlCl}_3$  addition (middle), and by sol-gel formation followed by  $\text{AlCl}_3$  addition (bottom) (modified from Ref. [73]).

31 Depending on the characteristics of the support materials different amounts of  
32 ionic liquid could be maintained on the surface following the order  $\text{SiO}_2 > \text{Al}_2\text{O}_3 >$   
33  $\text{TiO}_2 > \text{ZrO}_2$  after thorough extraction. As expected, low surface area and low surface  
34 OH group density in the latter supports result in poor loadings compared to silica  
35 and alumina. More importantly, pore damage was observed by X-ray diffraction in  
36 some structured supports, apparently by the hydrochloric acid formed in the catalyst  
37 preparation method. The possible effect on the catalytic performance of the catalysts  
38 in the presence of residual HCl from the preparation was not documented, but it  
39 can be assumed to be beneficial for the examined Friedel-Crafts reaction. Moreover,  
40 it was shown by leaching studies and examination of reaction filtrates that the ionic  
41 liquid catalyst loss was negligible. Consequently, the observed catalyst deactivation  
42 in recycling experiments was ascribed to moisture-induced catalyst degradation and  
43 the possible adsorption of reactants and by-products [67].

44 In an alternative synthetic approach, the formation of hydrochloric acid  
45 was avoided. The supported Lewis acidic ionic liquids were prepared by an

1 immobilization route involving the confinement of the ionic liquid's cation [73].  
2 Using this method, the cation of e.g. a chloride ionic liquid modified with an  
3 alkoxysilyl group, was covalently attached (i.e. grafted) to the surface. Then the  
4 chloride anion was transformed by  $\text{AlCl}_3$  to the Lewis acidic anion  $[\text{Al}_2\text{Cl}_7]^-$   
5 ((Scheme 5.6-1), middle). Soxhlet extraction of the supported ionic liquid cata-  
6 lyst after treatment with the aluminum chloride removed most of the unreacted  
7 reagent, and XRD analysis confirmed far less damage to structured supports than  
8 previously observed for the technique releasing HCl during synthesis.

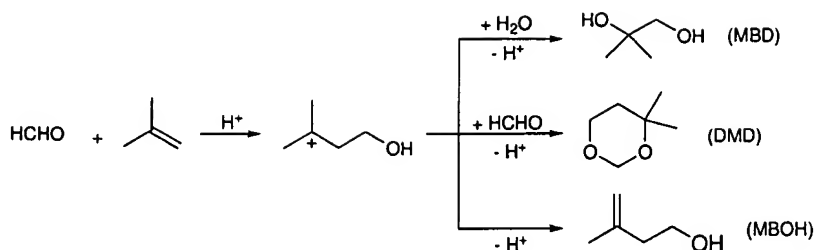
9 Comparison of results obtained from the alkylation of benzene with dodecene  
10 with the resulting catalysts made by the two immobilization methods revealed, in  
11 particular, excellent activity and selectivity for the materials obtained by cation graft-  
12 ing. Furthermore, these initial – but highly promising – results have been accompa-  
13 nied by an increased industrial interest for commercialization of these grafted ionic  
14 liquid catalyst systems. Johnson Matthey Catalysts recently announced (ICC Paris,  
15 July 2004) the commercialization of such grafted ionic liquid alkylation/acylation  
16 catalysts in late 2004, through their associated chemical company Alfa Aesar [74].

17 Alternatively, a sol-gel synthetic strategy has been reported for the preparation  
18 of a closely related type of supported Lewis acidic ionic liquid catalyst material  
19 ((Scheme 5.6-1), bottom), which subsequently was used for Friedel-Crafts alkyla-  
20 tions of benzene with dodecene [72]. Preparation first involved the formation of  
21 MCM-41 silica support material containing cationic imidazolium groups bonded  
22 to surface silicon atoms, by hydrothermal reaction between 1-(triethoxysilyl)propyl-  
23 3-methylimidazolium chloride and a mixture of tetraethylorthosilicate (TEOS) and  
24 dodecylamin. After removal of the amine template by Soxhlet extraction,  $\text{AlCl}_3$   
25 was introduced, leading to the Lewis acidic sol-gel catalyst. Using a comparable  
26 approach, ordered mesoporous silicas with hexagonal or lamellar structures incor-  
27 porating similar covalently bound ionic liquid species have also been synthesized  
28 recently [75].

29 Besides the already mentioned acidic aluminum chloride catalysts, alternative  
30 Friedel-Crafts catalysts such as supported acidic tin catalysts have also been de-  
31 veloped. The tin-based catalysts were prepared by a method which closely resem-  
32 bled the already mentioned two-step grafting method devised for the aluminum  
33 chloride catalyst. Here,  $\text{SnCl}_4$  was anchored on silica materials modified with  
34 tetraalkylammonium chloride moieties obtained for example, from reaction with [3-  
35 (trimethoxysilyl)propyl]octadecyldimethylammonium chloride, thereafter, reaction  
36 of the Lewis acid with the chloride moieties leads to formation of pentacoordinated  
37 anionic tin species forming catalytically active complexes (i.e.  $[\text{NR}_4][\text{SnCl}_5]$  species),  
38 associated with the surface. The supported tin catalysts were employed for con-  
39 densation reactions of olefins with aldehydes forming unsaturated alcohols (Prins  
40 condensation, Scheme 5.6-2) [76].

41 The condensation reactions between formaldehyde and isobutene using the acidic  
42 supported tin catalysts generally resulted in high selectivity (88–93%) for formation  
43 of the preferred product 3-methyl-3-butene-1-ol (MBOH). In addition, the catalysts  
44 were resistant to leaching of the active tin species showing no significant decrease in  
45 activity in two consecutive runs and no activity of the product filtrate. In comparison,

## 536 | 5 Organic Synthesis



**Scheme 5.6-2** Prins condensation of isobutene with formaldehyde (MBD: 3-methylbutane-1,3-diol, DMD: 4,4-dimethyl-1,3-diol, MBOH: 3-methyl-3-buten-1-ol catalyzed by tin(IV) chloride species (reproduced from Ref. [77]).

catalysts prepared by immobilizing  $SnCl_4$  directly on silica or by immobilizing preformed  $[N(Pr)_4][SnCl_5]$  on silica gave lower product selectivity. In addition, there was considerable leaching of tin species from the  $SnCl_4$ -silica catalysts.

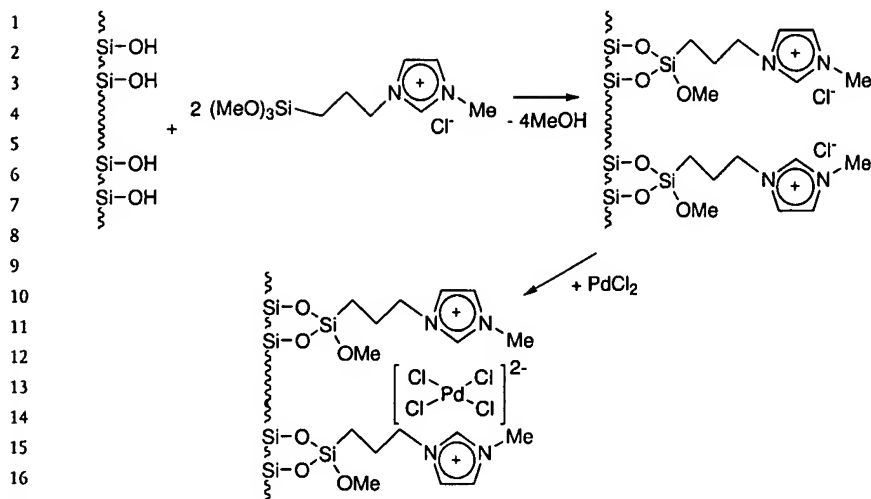
#### 5.6.2.3.2 Neutral, supported ionic liquid catalysts

A non-acidic supported palladium-based ionic liquid catalyst has also been prepared using the approach of attaching an ionic liquid cation to a support, followed by impregnation with a palladium complex. The catalyst was made by initial grafting of 1-(trimethoxysilylpropyl)-3-methylimidazolium chloride onto pre-dried silica followed by impregnation with  $PdCl_2$  [77] Scheme 5.6-3. For comparison, silica-supported  $PdCl_2$  catalyst and the homogeneous  $[BMIM]_2[PdCl]_4$  catalyst were also prepared.

The catalyst could be reused in three consecutive runs for Suzuki coupling reactions between derivatives of bromobenzenes and phenylboronic acid in *m*-xylene in the presence of different bases (e.g.  $K_2CO_3$ ), producing biphenyls in almost unchanged yields of 89–94%. The comparable yield using the supported  $PdCl_2$  catalyst was only 81%.

Structural parameter derivation from curve-fitting analysis of EXAFS spectra of the supported  $PdCl_2$  catalyst and the attached Pd catalyst, respectively, established the Pd–Cl distances in the catalysts to be almost the same, but with the latter having a higher palladium coordination number close to four (Table 5.6-2). This confirmed the quite uniform preparation of the attached catalyst on the support with mainly  $[PdCl_4]^-$  species present.

In another approach, heterogeneous olefin epoxidation catalysts were prepared by electrostatic attachment of binuclear peroxotungstate complexes onto an imidazolium-grafted silica support by ion-exchange [78]. The catalyst was made by initial grafting of the imidazolium-cations onto a pre-dried silica support by treatment with 1-octyl-3-(3-triethoxysilylpropyl)-imidazolium hexafluorophosphate. Analysis of the modified support by elemental analysis, IR and MAS-NMR confirmed the anchoring of the ionic liquid fragments and revealed the presence of



**Scheme 5.6-3** Preparation of grafted supported ionic liquid palladium catalyst (modified from Ref. [78]).

**Table 5.6-2** Structural parameters derived from EXAFS spectra of the Pd catalysts (from Ref. [78])

Catalyst	Shell	CN	R/Å	$\sigma^2/\text{\AA}^2$
Supported (PdCl <sub>2</sub> )	Pd-Cl	2.7 ± 0.2	2.32 ± 0.02	5 (± 2) × 10 <sup>-3</sup>
Attached (PdCl <sub>4</sub> <sup>-</sup> )	Pd-Cl	3.5 ± 0.1	2.31 ± 0.01	2.1 (± 0.3) × 10 <sup>-3</sup>

0.85 ionic liquid fragments per nm<sup>2</sup> on the support, and a number of reacted silanol groups corresponding to 54% of the original content. Afterwards, ion exchange of the [PF<sub>6</sub>]<sup>-</sup> ions with an aqueous solution of the potassium salt of a binuclear peroxotungstate complex containing [W(=O)(O<sub>2</sub>)<sub>2</sub>(H<sub>2</sub>O)]<sub>2</sub>(μ-O)]<sup>2-</sup> anions afforded the supported catalyst (105 μmol g<sup>-1</sup>), which contained the complex anion in its original structure (determined by Raman spectroscopy). Notably, the BET surface area of the support increased by 10% after the ion exchange (from 184 m<sup>2</sup> g<sup>-1</sup> to 203 m<sup>2</sup> g<sup>-1</sup>).

The supported peroxotungstate catalyst proved to be very efficient for the epoxidation of various olefins using H<sub>2</sub>O<sub>2</sub> (Fig. 5.6-5), with a catalytic activity comparable with a corresponding homogeneous tetraalkylammonium analog under the same conditions. The catalyst could be easily recovered by filtration and reused at least three times for the epoxidation of cyclooctene without loss of catalytic performance (99% yield, >99% selectivity). In accordance with this result no tungsten species

## 538 | 5 Organic Synthesis

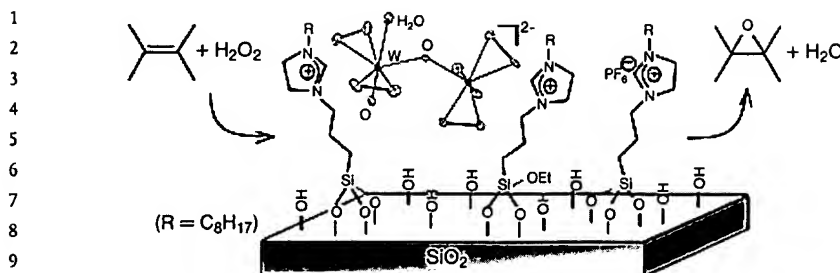
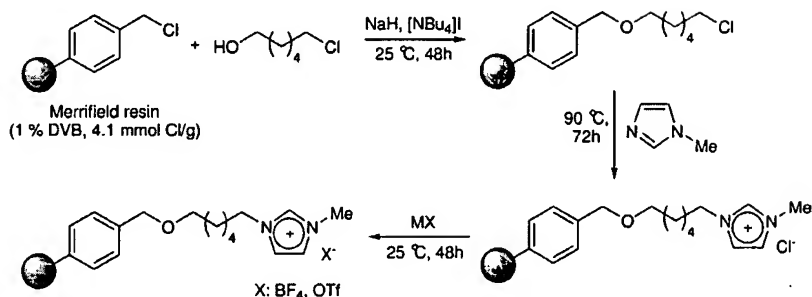


Fig. 5.6-5 Olefin epoxidation with  $\text{H}_2\text{O}_2$  using a supported ionic liquid catalyst containing an imidazolium-grafted silica support with electrostatic attached  $[\{\text{W}(=\text{O})(\text{O}_2)_2(\text{H}_2\text{O})_2(\mu\text{-O})\}]^{2-}$  complex anions (from Ref. [79]).



Scheme 5.6-4 Preparation of polymer-supported imidazolium salt catalysts, where DVB = divinylbenzene and MX =  $\text{NaBF}_4$  or KOTf (modified from Ref. [80]).

were detected in the filtrate after reaction by ICP-AES analysis (detection limit of 16 ppb).

Even though most of the supported ionic liquid catalysts prepared thus far have been based on silica or other oxide supports, a few catalysts have been reported where other support materials have been employed. One example involves a polymer-supported ionic liquid catalyst system prepared by covalent anchoring of an imidazolium compound via a linker chain to a polystyrene support [79]. Using a multi-step synthetic strategy the polymeric support (e.g. Merrifield resin among others) was modified with 1-hexyl-3-methylimidazolium cations (Scheme 5.6-4) and investigated for nucleophilic substitution reactions including fluorinations with alkali-metal fluorides of haloalkanes and sulfonylalkanes (e.g. mesylates, tosylates and triflates).

The polymer-supported catalysts proved to be reusable, efficient catalysts for particular fluorination of various substrates giving excellent yields (>90%), and much higher activity than obtained for systems containing the same amount of



1 ionic liquid in a system applying free ionic liquid. This observation was explained  
2 by a significantly increased nucleophilicity of the metal salt in the supported system  
3 compared with that obtained in conventional reaction systems, and proved to some  
4 extent to be cation dependent.

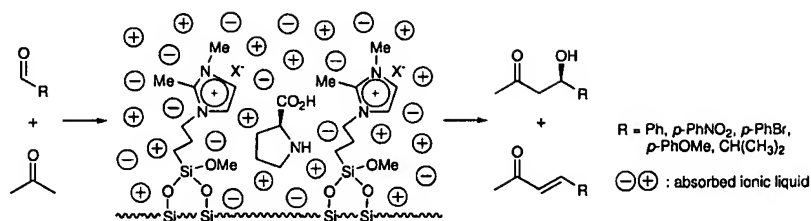
#### 5.6.2.4 Ionic Liquid Catalysts Supported through Physisorption or via Electrostatic Interaction

9 A second and somewhat simpler approach that can be applied to obtain supported  
10 ionic liquid catalyst systems involves the treatment of a solid, porous carrier material  
11 by a substantial amount of a catalytically active ionic liquid, allowing the reaction  
12 to take place in the dispersed phase. In these systems the ionic liquid phase can  
13 itself act as the catalytically active component or it may contain other dissolved  
14 compounds or reagents, for example, transition metal complexes, which function  
15 as the catalytically active species (i.e. generating SILP catalysts). Importantly, the  
16 ionic liquid catalyst phase in these SILP catalyst systems are confined to the carrier  
17 surface only by weak van der Waals interactions and capillary forces interacting  
18 in the pores of the support. In special cases electrostatic attachment of the ionic  
19 liquid phase may also be applied. Usually, the catalysts are prepared by traditional  
20 impregnation techniques, where a volatile solvent is used initially to reduce viscosity  
21 for the impregnation process and is finally removed by evaporation leaving the ionic  
22 catalyst solution dispersed on the support.

23 Preparation of SILP catalyst systems may, however, also include initial coverage  
24 of the support by covalently attached ionic liquid fragments corresponding to a  
25 monolayer-coverage to avoid some detrimental surface interaction. However, this  
26 additional treatment is often not necessary when the ionic liquids used are non-  
27 acidic and do not undergo reactions with the support surface. Therefore, catalysts  
28 containing neutral ionic liquids with relatively inert ions are usually applied for  
29 SILP catalyst applications as they are easier to prepare and to handle than the  
30 corresponding acidic ionic liquids (e.g. due to the sensitivity to hydrolysis of the  
31 latter). However, in this context it should not be forgotten that the frequently applied  
32 1,3-dialkylimidazolium cations may undergo carbene formation with basic supports  
33 or undesired metal-carbene formation under certain circumstances [80]. On the  
34 anion side, a general trend to avoid halogen-containing ions can be observed [81],  
35 since the presence of fluorine may be especially problematic, even if hydrolysis  
36 is not an issue. This is due to restricted disposal options and due to the elevated  
37 price of the hydrolysis stable fluorinated anions (e.g.  $[(CF_3SO_2)_2N]^-$ ,  $[CF_3SO_3]^-$ ,  
38  $[C_4F_9SO_3]^-$ ). Consequently, SILP catalysts employing halogen-free ionic liquids  
39 have been reported recently, as shown later.

##### 5.6.2.4.1 Supported ionic liquid catalysts (SILC)

43 In the simplest methodology using supported ionic liquid catalysts based on a non-  
44 bonding ionic liquid attachment to the support, the ionic liquid phase behaves both  
45 as reaction medium and catalyst.

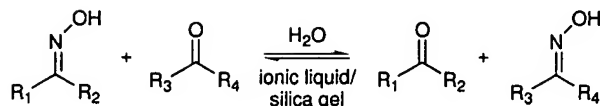


**Fig. 5.6-6** L-proline catalyzed aldol formation using supported ionic liquid phase asymmetric catalysis (reproduced from Ref. [83]).

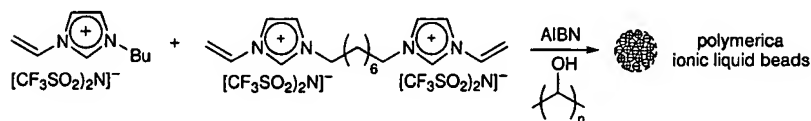
An approach using this method was applied to prepare a magnesium oxide supported choline hydroxide ionic liquid catalyst (choline hydroxide: (2-hydroxyethyl)trimethylimidazolium hydroxide) by impregnation [82]. The catalyst was used as a solid, basic catalyst for liquid-phase aldol condensation reactions of various carbonyl compounds forming products with interest for the pharmacological, flavor and fragrance industries. In several reactions a better catalyst performance (i.e. activity and product selectivity) was obtained using this SILC than the analogous homogeneous catalyzed reactions using choline or NaOH as catalyst, clearly demonstrating the potential of such catalysts for these C–C bonding reactions. However, no results from consecutive reactions or results from leaching studies have been reported for the catalyst at this stage.

In a related study, L-proline catalyzed asymmetric aldol condensation between aldehydes and ketones was examined using SILP asymmetric catalysts [83] (Fig. 5.6-6). In this approach, the catalysts were prepared by impregnation of [BMIM][PF<sub>6</sub>] ionic liquid containing L-proline directly onto a silica gel support, or by treatment of an additional amount of the ionic liquid containing L-proline onto a silica gel support pre-modified with a monolayer of ionic liquid attached to the carrier surface via grafting of the 1-(trimethoxysilylpropyl)-3-methylimidazolium cation (as shown earlier in Scheme 5.6-1, middle).

The catalytic performance of the SILC prepared by the different methods and containing various anions was compared with other L-proline supported catalysts and ionic liquid catalyst solutions containing L-proline for reactions between, for example, acetone and benzaldehyde. The results indicated that the surface of the silica gel must be functionalized with covalently attached ionic liquid in order to achieve yields and high *ees* (up to 64% *ee*), comparable with those obtained using analogous homogeneous (60% *ee*) or bulk ionic liquid systems (71–76% *ee*) containing L-proline. Moreover, it was realized that the additional phase of ionic liquid increased the yield, with the ionic liquid anion playing an important but not well understood role. Furthermore, the supported catalyst system containing an additional ionic liquid catalyst phase could be reused in three consecutive reactions with highly reproducible results. In another approach, a silica gel supported ionic liquid catalyst was prepared by the sol–gel technique from tetraethyl silicate in the presence of various ionic liquids including, for example, [R<sub>4</sub>MIM][X] (R = ethyl,



**Scheme 5.6-5** Supported ionic liquid catalyzed oxime transformation (reproduced from Ref. [84]).



**Scheme 5.6-6** Preparation of polymerized supported ionic liquid beads (modified from Ref. [86]).

butyl and decyl; X = [BF<sub>4</sub>]<sup>−</sup> and [PF<sub>6</sub>]<sup>−</sup>) [84]. The supported catalysts (containing 20–25 wt.% of the ionic liquids) were used to catalyze oxime transformations of various alkyl and aryl compounds (e.g. acetone and cyclohexanone oxime) in aqueous solvents by simultaneous C=N and C=O bond exchange (Scheme 5.6-5), and proved to give 10–20 times higher TONs than reactions performed using bulk ionic liquids as catalysts, which indicates some synergism between the ionic liquid and the support. Furthermore, it was realized that the presence of water was a key factor for obtaining high catalytic efficiency, which was explained by initial hydroxylamine formation from the reaction of water with the originally present oxime compound. Also here, no leaching studies were reported.

Also, in a closely related study, a similar sol–gel synthetic pathway was used to prepare silica gel supported ionic liquid deoxygenation catalysts from carboxylic acid-functionalized ionic liquids [85]. Here various aryl and alkyl oximes were converted into the corresponding oxo compounds with high conversions (up to 94% and excellent selectivity (>99%)) in aqueous acetone at room-temperature by co-production of 2-propanone oxime. TONs of up to 200 h<sup>−1</sup> obtained with the SILC were about four times higher than the TONs obtained using pure ionic liquids as catalysts.

Using a quite different approach, polymeric beads of supported ionic liquid palladium catalysts comprised of polymerized ionic liquid monomers and palladium complexes have been synthesized using traditional suspension polymerization methods [86]. Here, polymeric ionic liquid beads were made from polymerization of 1-butyl-3-vinylimidazolium bis[(trifluoromethyl) sulfonyl]imide and poly(vinylalcohol) by heating with AIBN (2,2′-azobis(2-methylpropionitrile)) in the presence of 1,1′-bis[1,8-octyl]-3-vinylimidazolium bis[(trifluoromethyl) sulfonyl]amide as cross-linker (Scheme 5.6-6). The ionic liquid support beads proved to be thermally stable up to 250 °C which is significantly higher than conventional vinyl resins.

After impregnation of the polymeric support material with palladium(II) tri-(*o*-tolyl)phosphine complexes the resulting catalyst material was tested in the Heck coupling of bromobenzene with butyl acrylate in DMF to yield 75% of *E*-3-phenylacrylic

## 542 | 5 Organic Synthesis

1 acid butyl ester product. Analysis (ICP-MS) of the filtrate after the reaction revealed,  
2 however, leaching of 1–2 ppm palladium metal from the catalyst. Additionally, the  
3 [BTA]<sup>−</sup> anion could readily be ion exchanged with other anions of catalytic interest  
4 (e.g. [CoCl<sub>4</sub>]<sup>−</sup>) by passing a solution of 1-decyl-3-methyl imidazolium tetrachloro-  
5 cobaltate through a column of the polymeric beads, thus indicating the potential  
6 for rapid catalyst modifications in these systems.

#### 8 5.6.2.4.2 Supported ionic liquid phase (SILP) catalysts incorporating metal complexes

9 When a substantial amount of an ionic liquid is immobilized on a support, the  
10 formation of a film of free ionic liquid on the carrier may act as an inert reaction  
11 phase to dissolve various homogeneous catalysts [87]. This further implies that  
12 although the resulting material appears as a solid, the active species dissolved in  
13 the ionic liquid phase on the support still comprises the attractive features of a  
14 dissolved homogeneous catalyst, for example, high specificity and uniform nature  
15 of the catalytically active sites.

16 In the first reported example using this approach, supported hydroformylation  
17 catalysts were prepared by impregnation of a surface-modified silica gel containing  
18 covalently anchored ionic liquid fragments with ionic liquid solutions of the precursor  
19 [Rh(acetylacetonate)(CO)<sub>2</sub>] and the trisulfonated triphenylphosphine ligand as  
20 either trisodium salt (TPPTS) or as (1-butyl-3-methylimidazolium) salt (TPPTI)  
21 (ligand/Rh ratio of 10) [88]. The ligand TPPTI was found to dissolve in both  
22 [BMIM][BF<sub>4</sub>] and [BMIM][PF<sub>6</sub>], while the corresponding sodium salt only dissolved  
23 in [BMIM][BF<sub>4</sub>].

24 The initial preparation of the catalyst involved modification of a pre-dried silica gel  
25 support by treatment of the support in an immobilizing step with functionalized  
26 ionic liquids, such as 1-butyl-3-(3-triethoxysilylpropyl)imidazolium tetrafluoroborate  
27 or hexafluorophosphate. Analysis of the surface coverage revealed an average  
28 of 0.4 ionic liquid fragments per nm<sup>2</sup>, corresponding to the involvement of approximately  
29 35% of all the hydroxy groups of the pre-treated silica gel. Treatment of  
30 the obtained support with additional ionic liquid resulted in a free film of ionic  
31 liquid on the support corresponding to an ionic liquid phase loading of 25 wt.%.  
32 After solvent removal under reduced pressure, a slightly yellow-colored powder was  
33 obtained.

34 The prepared catalysts were investigated for the hydroformylation of 1-hexene  
35 to produce heptanal in a batch-wise, liquid phase reaction (Table 5.6-3), and all  
36 results obtained were compared to the identical reaction in the liquid–liquid biphasic  
37 process design.

38 A comparison between the supported [BMIM][BF<sub>4</sub>]-based catalyst and the biphasic  
39 ionic liquid reaction showed that the supported system exhibited a slightly  
40 enhanced activity (TOF of 65 min<sup>−1</sup> versus 23 min<sup>−1</sup>) due to the higher concentration  
41 of rhodium complexes at the interface and the generally larger interface  
42 of the supported system. As expected for the applied mono-phosphine ligand, low  
43 selectivities (n/iso-heptanal ratios) of 2.4 to 2.5 were obtained. Importantly, at high  
44 aldehyde concentrations the ionic liquid [BMIM][BF<sub>4</sub>] was found to partially dissolve  
45 in the organic phase leading to a considerable rhodium loss of up to 2.1 mol%. The

Table 5.6-3 Evaluation of the hydroformylation reaction of 1-hexene to form n,iso-heptanal using supported ionic liquid phase catalysis (SILP), biphasic catalysis and homogeneous catalysis (reproduced from Ref. [88])

Entry	Condition <sup>[a]</sup> /ligand	Solvent	Time/min	Yield (%)	n/iso	TOF <sup>[b]</sup> /min <sup>-1</sup>
1	SILP/TPPTI	[BMIM][BF <sub>4</sub> ]	300	33	2.4	65
2	SILP/TPPTS	[BMIM][BF <sub>4</sub> ]	240	40	2.4	56
3	SILP/TPPTI	[BMIM][PF <sub>6</sub> ]	270	46	2.4	60
4	SILP/no ligand	[BMIM][PF <sub>6</sub> ]	180	85	0.4	190
5	biphasic/TPPTI	[BMIM][BF <sub>4</sub> ]	230	58	2.2	23
6	biphasic/TPPTI	[BMIM][PF <sub>6</sub> ]	180	70	2.5	22
7	biphasic/TPPTS	H <sub>2</sub> O	360	11	23	2.4
8	homog./PPh <sub>3</sub>	toluene	120	95	2.6	400

<sup>a</sup> Reaction conditions: All runs were conducted at 100 °C with a Rh/ligand ratio of 1:10, SILP runs were evaluated in a 70 ml autoclave at 1500 psi (100 bar) and biphasic and homogeneous catalyst systems were evaluated in a 300 ml autoclave at 600 psi (40 bar).

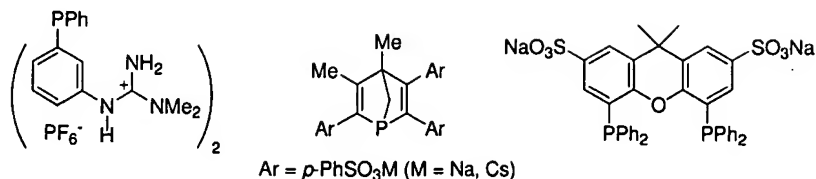
<sup>b</sup> TOF defined as mol(aldehyde) per mol(rhodium) per minute (full reaction time).

metal loss could be somewhat suppressed at lower aldehyde concentrations and higher ligand excess in single runs. However, pronounced catalyst deactivation was found, even at lower conversion, during recycling of the catalyst independent of the presilylation of the support [89].

Hydroformylation of 1-hexene has also recently been performed using a MCM-41 supported Rh-TPPTS catalyst based on the ionic liquid 1,1,3,3-tetramethylguanidinium lactate (TMGL) [90]. Here the catalysts exhibited practically unchanged performance in twelve consecutive runs providing about 50% conversion and also low n/iso ratios of ca. 2.5.

In a continuing effort to explore the full technical potential of supported ionic liquids the concept has been extended to continuous flow processes. The reactions studied were Rh-phosphine catalyzed hydroformylation of propene and 1-octene using more technically attractive continuous flow fixed-bed reaction designs [91–93] (more detailed description of the reaction set-ups may be found in Refs. [94, 95] for gas-phase reactions and in Ref. [96] for liquid-phase reactions).

The supported ionic liquid phase catalyst systems were primarily prepared by immobilizing [Rh(acetylacetonate)(CO)<sub>2</sub>] and the applied phosphine ligands in a film of either [BMIM][PF<sub>6</sub>] or [BMIM][n-C<sub>8</sub>H<sub>17</sub>OSO<sub>3</sub>] ionic liquid on silica gel (either dried or partly dehydroxylated by thermal treatment), by using impregnation with degassed solutions of methanol or water–dichloromethane. This procedure allowed the generation of catalysts with varying ligand/rhodium ratios and ionic liquid loadings. Further addition of silica gel resulted in a catalyst rhodium metal loading of 0.2 wt.%. Three different phosphine ligands were used for the preparation of the supported catalyst, all modified with charged groups to increase the ionic liquid solubility (Fig. 5.6-7).



**Fig. 5.6-7** The charged phosphine ligands bis(*m*-phenylguanidinium)phenylphosphine hexafluorophosphate, guanidinium (a), tricesium 3,4-dimethyl-2,5,6-tris(*p*-sulfonatophenyl)-1-phosphanorbornadiene, NORBOS (b) and disodium 4,5-bis(diphenylphosphino)-2,7-bis(sulfonato)-9,9-dimethylxanthene, sulfoxantphos (c), examined for supported ionic liquid phase continuous Rh-catalyzed propene hydroformylation [91–93].

In an application for continuous biphasic, liquid–liquid 1-octene hydroformylation using a SILP Rh-NORBOS catalyst containing [BMIM][PF<sub>6</sub>], a steady catalyst performance (TOF of 44 h<sup>−1</sup> and *n*/*iso* ratio of 2.6) was achieved after 3–4 h of reaction. Furthermore, no leaching of rhodium metal could be detected by ICP-AES analysis of outlet samples, at least after this relatively short reaction time.

In more comprehensive studies, the catalytic performance of the silica-supported catalyst based on the different ligands was found essentially not to be influenced by the type of ionic liquid in the gas-phase propene hydroformylation reactions, as no significant differences were observed with [BMIM][PF<sub>6</sub>] or [BMIM][*n*-C<sub>8</sub>H<sub>17</sub>OSO<sub>3</sub>] being the ionic liquids applied (except for the catalyst preformation which appeared to depend on the solubility of the ligand and precursor). Furthermore, this was also shown to be the case in a study performed with analogous catalysts based on alternative oxide supports such as titania, alumina and zirconia [97]. In Table 5.6-4 the most relevant results for the hydroformylation of propene with the different catalyst systems based on the ionic liquid [BMIM][PF<sub>6</sub>] and pre-dried silica support are compiled.

The performance of the catalyst in 5 h reactions was found to be drastically influenced by the catalyst composition with respect to ligand/rhodium ratio and ionic liquid loading. When using catalysts with low ligand to rhodium ratios, only low selectivity for the linear product was obtained (entries 1 to 3 and 8 to 10). This was ascribed, in part, to the presence of most of the active rhodium species as ligand-free, less selective complexes under these conditions. Additionally, an increased ionic liquid loading led to a decrease in activity, which indicated that the catalysts were operating under certain mass-transfer limitations. In accordance with this, the highest activities were initially observed for the ionic liquid free catalysts (entries 1, 6, 8 and 11).

The use of catalyst systems containing the bidentate phosphine ligand sulfoxantphos proved particularly interesting, as excellent *n*/*iso* ratios of 23 (i.e. linear product selectivities up to 96%) were attained with these systems (entries 12 to 14). Remarkably, at a low ligand/rhodium ratio of 2.5 (entries 9 and 10), the selectivity of the

Table 5.6-4 Continuous, gas-phase Rh-phosphine catalyzed propene hydroformylation using silica gel-based supported ionic liquid phase catalysts containing [BMIM][PF<sub>6</sub>]<sup>[a]</sup> (compiled from Refs. [91] and [92])

Entry	Ligand	L/Rh <sup>[b]</sup>	Ionic liquid loading		TOF <sup>[d]</sup> (h <sup>-1</sup> )	n/iso <sup>[e]</sup>	Linearity (%)
			wt. %	$\alpha$ <sup>[c]</sup>			
1	guanidinium	2.9	–	0.00	55.5	0.9	47.4
2	guanidinium	2.9	108.4	0.78	20.6	0.9	47.4
3	guanidinium	2.9	138.9	1.00	16.8	1.0	50.0
4	NORBOS-Cs	11.3	6.9	0.05	88.4	2.0	66.7
5	NORBOS-Cs	11.3	20.8	0.15	79.4	1.3	56.5
6	NORBOS-Cs	21.4	–	0.00	45.8	2.8	73.8
7	NORBOS-Cs	21.3	6.9	0.05	28.2	2.6	72.2
8	sulfoxantphos	2.5	–	0.00	37.4	1.7	63.0
9	sulfoxantphos	2.4	23.6	0.17	1.5	1.8	64.0
10	sulfoxantphos	2.5	68.1	0.49	5.1	2.0	66.4
11	sulfoxantphos	10.2	–	0.00	40.8	16.9	94.4
12	sulfoxantphos	10.0	25.0	0.18	34.9	22.6	95.8
13	sulfoxantphos	10.0	72.2	0.52	25.4	22.0	95.8
14	sulfoxantphos	20.0	27.8	0.20	16.7	23.7	96.0
15 <sup>[f]</sup>	–	–	105.6	0.76	–	–	–

<sup>a</sup> Reaction conditions: Propene:CO:H<sub>2</sub> = 1:1:1, T = 100 °C, p = 5 bar for guanidinium and NORBOS-Cs, p = 10 bar for sulfoxantphos, reaction time = 5 h. Supported catalysts: 0.2 wt. % rhodium metal, dried silica gel (110 °C, 24 h, in vacuo), [BMIM][PF<sub>6</sub>] used for impregnation.

<sup>b</sup> Molar ligand to metal ratio.

<sup>c</sup> Ratio of ionic liquid volume to support pore volume.

<sup>d</sup> Mol butanal per mol rhodium per hour.

<sup>e</sup> Ratio between linear and branched butanal.

<sup>f</sup> Support loaded with ionic liquid only.

Rh-sulfoxantphos system was significantly lower and comparable to the best selectivity obtained with the monodentate phosphines. This results was in contrast to analogous experiments performed in ionic liquid–liquid biphasic mode where high selectivities were obtained [81, 98], and suggested some ligand loss due to reactions between the ligand and the solid surface.

Importantly, it was also realized in these initial studies that the catalysts deactivated in prolonged use with simultaneous decrease in catalytic activity and selectivity, independent of the type of ionic liquid, ionic liquid loading  $\alpha$ , and the ligand/rhodium ratio of the system. However, additional studies demonstrated a suitable thermal pre-treatment of the silica support to be necessary to obtain stable SILP catalysts. This technique was applied to prepare Rh-sulfoxantphos catalysts with [BMIM][n-C<sub>8</sub>H<sub>17</sub>OSO<sub>3</sub>] and similar systems without ionic liquid. Both systems were compared in 60 h continuous propene hydroformylation reactions using similar conditions as previously reported (Table 5.6-4, entries 11 and 12, Fig. 5.6-8) [93].

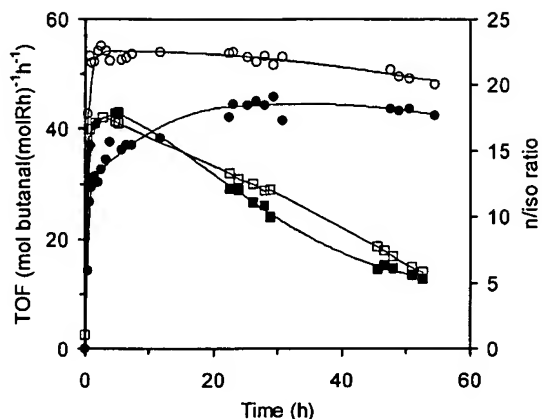


Fig. 5.6-8 Continuous hydroformylation of propene with silica Rh-sulfoxantphos/[BMIM][ $n\text{-C}_8\text{H}_{17}\text{OSO}_3$ ] catalysts (ligand/rhodium = 10) having ionic liquid loadings of  $\alpha = 0$  ( $\square$ ,  $\blacksquare$ ) and  $\alpha = 0.1$  ( $\circ$ ,  $\bullet$ ). Activity (closed symbols) and selectivity (n/iso ratio, open symbols) (modified from Ref. [93]).

In the reaction using the Rh-sulfoxantphos catalyst without ionic liquid, the activity and selectivity decreased sharply after 5–10 h on stream, while the SILC system ( $\alpha = 0.1$ ) reached its maximum activity only after 30 h and maintained this level stable up to 60 h (i.e. TON > 2400) along with a high selectivity corresponding to a n/iso ratio of 21–23. It can also be deduced that the apparently negative ionic liquid effect on the catalyst activity measured in the short time reactions can be explained by a delayed formation of the catalytically active species.

Besides the importance of the ionic liquid solvent, it was also shown that a relatively large excess of sulfoxantphos ligand is required to obtain a stable catalyst system, even in reactions using a thermally pre-treated support. This aspect was further recognized by solid-state  $^{29}\text{Si}$  and  $^{31}\text{P}$  MAS-NMR measurements to be directly related to an irreversible reaction of the ligand with the acidic silanol surface groups during catalysis. Moreover, FT-IR measurements on the supported catalysts under synthesis gas at catalytically relevant conditions, verified the complex formation in the supported ionic liquid phase to be similar to that observed for Rh-sulfoxantphos and analogous xanthene ligand-based rhodium complexes in organic and ionic liquid solvents (Table 5.6-5) [99]. This proved that the studied reactions are indeed homogeneously catalyzed, as expected.

Finally, the FT-IR examinations established the catalyst instability to be associated with degradation of the co-existing isomeric  $[\text{HRh}(\text{CO})_2(\text{sulfoxantphos})]$  complexes, which in turn is correlated to the accessible amount of ligand available for complex formation. Thus, the prerequisites for obtaining an active, highly selective, and durable SILP hydroformylation catalyst, were shown to involve both the presence of ionic liquid solvent and a relatively large excess of bisphosphine ligand



**Table 5.6-5** Comparison of infrared  $\nu(\text{CO})$  bands in  $[\text{HRh}(\text{CO})_2(\text{L})]$  complexes in different systems (reproduced from Ref. [93])

	Solvent	ea-isomer $\nu(\text{CO})$ ( $\text{cm}^{-1}$ )	ee-isomer $\nu(\text{CO})$ ( $\text{cm}^{-1}$ )
SILP Rh-sulfoxantphos	[BMIM][n-C <sub>8</sub> H <sub>17</sub> OSO <sub>3</sub> ]	1994, 1948	2035(w), 1964
[HRh(CO) <sub>2</sub> (sulfoxantphos)] <sup>[a]</sup>	[BMIM][PF <sub>6</sub> ]	1985, 1935	2032, 1967
[HRh(CO) <sub>2</sub> (xantphos)] <sup>[a]</sup>	benzene	1991, 1941	2036, 1969
[HRh(CO) <sub>2</sub> (thixantphos)] <sup>[a]</sup>	cyclohexane	1999, 1953	2040, 1977

<sup>a</sup> Ref. [99].

to compensate for some detrimental surface reactions. In another example, a SILP hydrogenation catalyst was prepared by confining a [BMIM][PF<sub>6</sub>] ionic liquid phase containing [Rh(norbornadiene)(PPh<sub>3</sub>)<sub>2</sub>][PF<sub>6</sub>] complexes onto the carrier by impregnation (contained 25 wt.% ionic liquid, corresponding to an average ionic liquid catalyst layer of 6 Å) [100]. This catalyst was used for liquid-phase hydrogenations of e.g. 1-hexene and compared to analogous reactions performed in bulk ionic liquid or organic media with the same Rh-complex. A superior activity of the SILP catalysts was revealed with up to 100 times higher TOF under similar reaction conditions. This enhanced activity was attributed to its higher interfacial complex concentration. Moreover, the SILP catalyst showed excellent durability and was reused for 18 consecutive runs without any significant loss of activity and without indication of rhodium metal leaching (the level remained below the detection limit of 33 ppb).

In a different approach, supported ionic liquid poly(vinylidene fluoride) membranes containing an active phase of [Rh(norbornadiene)(PPh<sub>3</sub>)<sub>2</sub>][PF<sub>6</sub>] complex dissolved in different ionic liquids with fluorinated anions (e.g. [RMIM][X] (R = ethyl, butyl and X = [BF<sub>4</sub>]<sup>-</sup>, [PF<sub>6</sub>]<sup>-</sup>, [(CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>N]<sup>-</sup> and [CF<sub>3</sub>SO<sub>3</sub>]<sup>-</sup>), were employed to examine the hydrogenation of propene and ethane [101]. To accomplish the hydrogenation reactions, the olefin was maintained at atmospheric pressure on the feed side of the membrane, while a flow of hydrogen gas at the same pressure was swept over the permeate side to remove hydrogenated products when these had passed through the catalytic ionic liquid bulk phase of the membrane (Fig. 5.6-9).

The maximum hydrogenation rates for the catalytic membrane materials based on the different ionic liquids was found to follow the order [EMIM][(CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>N]] > [EMIM][CF<sub>3</sub>SO<sub>3</sub>] > [EMIM][BF<sub>4</sub>] > [BMIM][PF<sub>6</sub>], which proved to be different from the relative gas solubilities estimated from gas permeability studies in the liquids. However, the order of reactivity was in line with results previously found for some of the ionic liquids in analogous biphasic liquid-liquid hydrogenation of 1-pentene [102], which showed the importance of the coordination strength of the ionic liquid anions on reaction rates.

Supported ionic liquid phase hydrogenation catalysts based on a polymeric poly(allyldimethylammonium chloride) support have also been prepared by attachment of [BMIM][PF<sub>6</sub>] solutions of [RhCl(PPh<sub>3</sub>)<sub>3</sub>] (Wilkinson

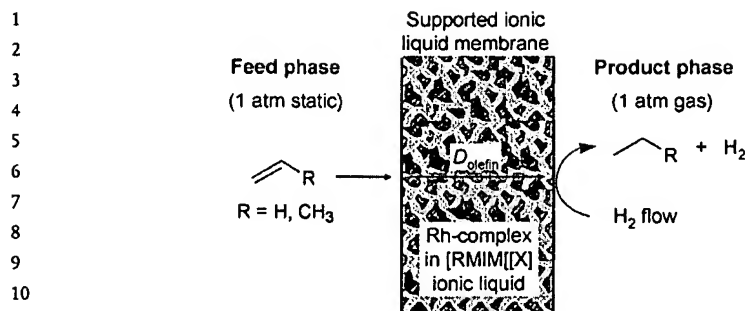


Fig. 5.6-9 Schematic illustration of olefin hydrogenation with a supported ionic liquid poly(vinylidene fluoride) membrane containing [Rh(norbornadiene)(PPh<sub>3</sub>)<sub>2</sub>][PF<sub>6</sub>] complexes.

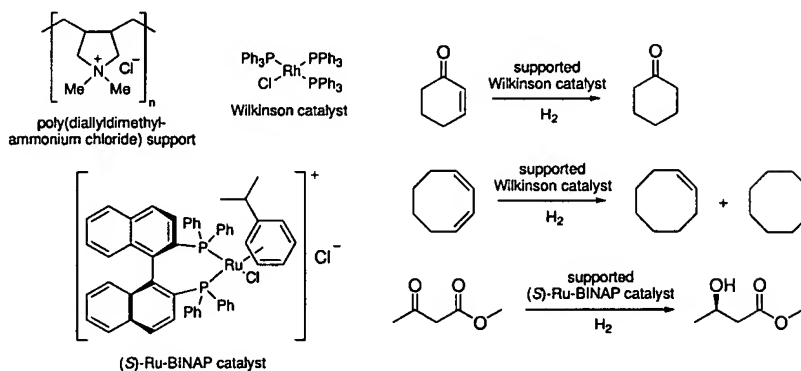
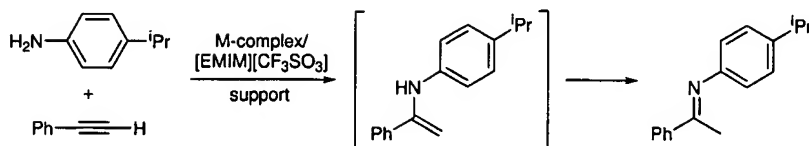


Fig. 5.6-10 Hydrogenation reactions using poly(diallyldimethylammonium chloride) supported ionic liquid phase catalysts (reproduced from Ref. [103]).

catalyst) and [RuCl(S-BINAP)]Cl (chloro-[(S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-biphenyl](isopropylbenzene)-ruthenium(II)-chloride), respectively [103]. The supported catalysts were applied for liquid-phase hydrogenations of 2-cyclohexen-1-one and 1,3-cyclooctadiene and asymmetric hydrogenation of methyl acetoacetate (Fig. 5.6-10).

For all reactions studied, the activity of the supported catalysts was higher than for the similar biphasic ionic liquid system, which was ascribed to improved mass transfer between the substrates and the ionic liquid phase. In addition, the observed product selectivities of 64–87% and enantioselectivity of 97% for the SILP-Ru-(S)-BINAP catalyzed reaction equalled those of the homogeneous reference reactions. No indication of rhodium metal leaching was found by AAS analysis of the reaction filtrate.



**Scheme 5.6-7** Synthesis of (4-isopropylphenyl)-(1-phenylethylidene)-amine by hydroamination of phenylacetylene with 4-isopropylamine using supported ionic liquid phase metal catalysts (reproduced from Ref. [104]).

Catalytic hydroamination is another type of reaction, that has been recently tested using the concept of SILP catalysis containing late transition metal complexes [104]. In the study, hydroamination of phenylacetylene was carried out by direct addition of 4-isopropylamine (Scheme 5.6-7) using different supported catalysts obtained by shock freezing (followed by freeze-drying) a mixture of [EMIM][CF<sub>3</sub>SO<sub>3</sub>]-dichloromethane solutions of cationic rhodium(I), palladium(II), copper(I) and zinc(II), respectively, containing a macroporous, diatomé earth support (Chromosorb P, pre-modified by dichlorodimethylsilane treatment, i.e. silylated) in liquid nitrogen.

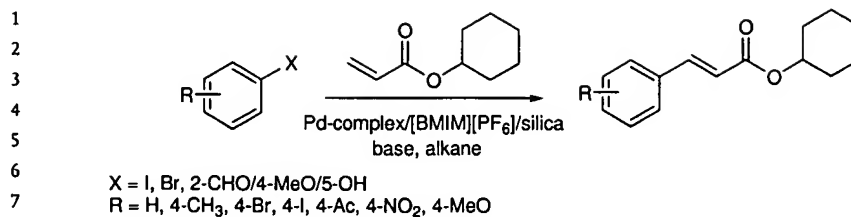
For the SILP catalyst containing the complexes [Rh(DPPF)(2,5-norbornadiene)][ClO<sub>4</sub>], [Pd(DPPF)][CF<sub>3</sub>SO<sub>3</sub>]<sub>2</sub> and Zn[CF<sub>3</sub>SO<sub>3</sub>]<sub>2</sub> (DPPF: 1,1'-bis-(diphenylphosphino)-ferrocene), the rate of reaction was found to be 2–6 times higher than in the corresponding homogeneous catalyzed reactions. In contrast, for the SILP-[Cu<sub>2</sub>(C<sub>6</sub>H<sub>5</sub>CH<sub>3</sub>)] [CF<sub>3</sub>SO<sub>3</sub>]<sub>2</sub> catalyst a significantly lower catalytic activity was observed than for the corresponding homogeneous system, possibly due to competing coordination of the ionic liquid and the substrate for the copper(I) center. Notably, product selectivity (85–100%) was also significantly increased for all four supported catalysts compared to the homogeneous reactions.

Pd-complexes have also been impregnated on an amorphous silica support with the aid of a solution containing [BMIM][PF<sub>6</sub>] dissolved in tetrahydrofuran and these systems were applied as highly efficient catalysts for promoting Heck coupling reactions between various aryl halides and cyclohexyl acrylate in alkanes without the presence of additional ligand (Scheme 5.6-8) [105].

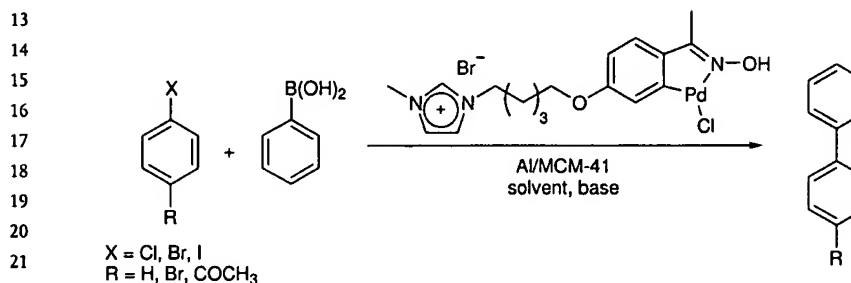
With optimized reaction conditions using a supported Pd(acac)<sub>2</sub>-containing catalyst, a TOF of 8000 h<sup>-1</sup> was reached in the reaction of iodobenzene with cyclohexyl acrylate in n-dodecane using tri-n-butylamine as base. Moreover, the catalyst could readily be reused up to six times giving yields of 89–98% without taking any precautions (e.g. avoidance of air), if surface deposited tri-butylammonium iodide salt was removed by washing with aqueous sodium hydroxide at an intermediate stage during the consecutive reactions. ICP-analysis of the organic product layer after reaction revealed only depletion of trace amounts of palladium metal (less than 0.24%) from the supported ionic liquid catalyst phase.

In another approach, an oxime carbapalladacycle ionic liquid catalyst was attached to an aluminosilicate support (Al/MCM-41, Si/Al 13) via electrostatic interaction by

## 550 | 5 Organic Synthesis



9 **Scheme 5.6-8** Pd-catalyzed Mizoroki-Heck coupling reactions between  
10 aryl halides and cyclohexyl acrylate in alkanes using silica/[BMIM][PF<sub>6</sub>]  
11 supported ionic liquid phase catalysts (reproduced from Ref. [105]).



23 **Scheme 5.6-9** Base-promoted Suzuki cross-coupling of halobenzenes  
24 and phenylboronic acid using Al/MCM-41-supported oxime  
25 carbapalladacycle ionic liquid catalyst (reproduced from Ref. [106]).

26  
27  
28 impregnation, and tested for base-promoted Suzuki cross coupling of haloben-  
29 zenes and phenylboronic acid in toluene and dimethylformamide, respectively  
30 (Scheme 5.6-9) [106].

31 The performance of the supported palladium ionic liquid catalyst was found to  
32 be very dependent on the organic solvent, revealing higher activity (comparable  
33 to analogous homogeneous catalyzed reactions) and higher product selectivity to-  
34 wards Suzuki-coupled products compared to homo-coupled products in a polar  
35 solvent such as DMF (no homo-coupled products observed) than in toluene (1:2  
36 to 1:5 distribution of products). Also, using the catalyst in DMF, coupling of less  
37 reactive bromo- and chlorobenzenes proved possible. Unfortunately, it was also  
38 shown that the catalyst could only be reused for a few consecutive runs with similar  
39 activity (resulting in 86–90% conversion) and selectivity, due to the partial insta-  
40 bility of the oxime carbapalladacycle complex under the reaction conditions. In  
41 a different approach based on membrane technology, oligomerization of ethene  
42 has also been examined using a poly(ethersulfone)-supported ionic liquid mem-  
43 brane containing [EMIM]Cl–AlCl<sub>3</sub> ionic liquids with or without the presence of  
44 [NiCl<sub>2</sub>{P(cyclohexyl)<sub>3</sub>}]<sub>2</sub> dimerization catalyst and dichloroethylaluminate as an acid  
45 scavenging co-catalyst [107].

**Table 5.6-6** Pd-catalyzed hydrogenation reactions, with nanoparticles actively supported on molecular sieves with a TMGL layer (reproduced from Ref. [109])

Entry	Olefins	Olefin/Pd molar ratio	T (°C)	t (h)	Conv. (%)	TOF (min <sup>-1</sup> )
1 <sup>[a]</sup>	cyclohexene	12000	20	10	100	20.0
2	cyclohexene	12000	40	7	100	28.3
3 <sup>[b]</sup>	cyclohexadiene	12000	20	3	98	65.3
4	1-hexene	12000	20	3	100	66.7
5 <sup>[c]</sup>	1-hexene	120	20	6	100	0.30
6 <sup>[d]</sup>	cyclohexene	500	40	5	100	1.67
7 <sup>[e]</sup>	cyclohexene	12000	20	10	100	20.0
8 <sup>[f]</sup>	cyclohexene	12000	20	10	100	20.0
9 <sup>[g]</sup>	cyclohexene	12000	20	10	100	20.0
10 <sup>[h]</sup>	cyclohexene	12000	20	10	100	20.0

<sup>a</sup> The product was cyclohexane.

<sup>b</sup> The product was cyclohexene; no cyclohexane was detected.

<sup>c</sup> Based on data from G. Schmid, *Chem. Rev.*, 1992, 92, 1709 and G. Schmid, M. Harm, *J. Am. Chem. Soc.*, 1993, 115, 2047, using a heterogeneous catalyst with phenanthroline-protected Pd nanoparticles.

<sup>d</sup> The reaction was carried out using Pd nanoparticles in 1-butyl-3-methylimidazolium hexafluorophosphate as the catalyst, see Ref. [110].

<sup>e-h</sup> The catalyst was used a second, third, fourth, and fifth time, respectively, after the experiment described in entry 1.

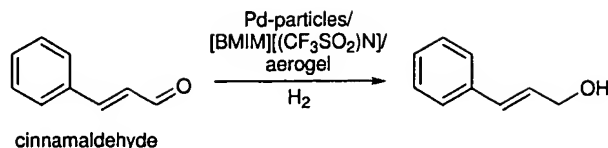
#### 5.6.2.4.3 Supported ionic liquid catalyst systems containing metal nanoparticles

Ionic liquids often induce low interfacial tensions when combined with other phases [108]. This characteristic results in high nucleation rates that can be applied to generate metallic nanoparticles that are further stabilized to a high extent, preventing particle aggregation. This very interesting property has recently been used for the first time to prepare a molecular sieve (Al:Si = 1:1) SILP catalyst containing Pd nanoparticles (diameter of most particles 1–2 nm as determined by TEM) which were stabilized by the ionic liquid 1,1,3,3-tetramethylguanidinium lactate (TMGL) [109]. Here, the alkaline nature and the ability of the guanidinium ions to coordinate metal particles were combined to make a stable catalytic material containing 20 wt.% (corresponding to an average supported ionic liquid layer of 0.4 nm) of a strongly absorbed ionic liquid phase. Notably, the palladium nanoparticles were larger than the average thickness of the ionic liquid layer, thus leaving part of the particles less covered by the ionic liquid.

The supported nanoparticle catalyst system was used for solvent-free hydrogenation reactions of cyclohexene, 1-hexene, and 1,3-dicyclohexadiene, respectively, and compared with a similar biphasic ionic liquid system and with a heterogeneous supported nanocatalyst (Table 5.6-6).

The supported ionic liquid nano-catalysts showed unprecedented activity (entries 1 to 4) and high selectivity for the hydrogenation of cyclohexadiene to cyclohexene (entry 3). This was attributed to a much stronger absorption of the hexadiene to the Pd particles than the cyclohexene, resulting in preferential hydrogenation of the

## 552 | 5 Organic Synthesis



7 **Scheme 5.6-10** 2,4-hydrogenation of cinnamaldehyde using  
8 aerogel-supported ionic liquid catalyst material containing palladium  
9 nanoparticles (reproduced from Ref. [112]).

10  
11 alkadiene compared to the alkene. Additionally, the supported ionic liquid catalyst  
12 could be reused for another four runs without any loss of activity (entries 7 to  
13 10). Moreover, no palladium metal leaching to the organic products (determined  
14 by AAS) and no metal particles aggregation into larger particles on the molecular  
15 sieves (determined by TEM) was observed. Thus, the combination of palladium  
16 nanoparticles, ionic liquid and molecular sieves revealed an excellent synergistic  
17 effect to enhance the activity and durability of the catalyst.

18 Also, using a closely related approach, an aerogel-supported catalyst material con-  
19 taining palladium nanoparticles was made by an ionic liquid mediated synthesis,  
20 which previously had proved to be a convenient and effective way of preparing  
21 silica aerogel materials [111]. The synthesis involved initial formation of palla-  
22 dium(0) colloids (approximate diameter 1 nm) from Pd(acetate)<sub>2</sub> and triphenylphos-  
23 phine in [BMIM][(CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>N] followed by incubation with tetraethylorthosilicate  
24 (TEOS) and formic acid. After gelation and aging, most of the ionic liquid sol-  
25 vent was, however, removed by Soxhlet extraction with acetonitrile, resulting in  
26 an apparently dry monolithic catalyst material containing highly dispersed Pd  
27 nanoparticles [112]. The catalyst was tested for liquid-phase hydrogenation of an  
28 α,β-unsaturated aldehyde (cinnamaldehyde) into the corresponding unsaturated al-  
29cohol (Scheme 5.6-10), and for Heck coupling of iodobenzene with butyl acrylate in  
30 DMF.

31 In these reactions the catalyst proved very active (TOF up to 1307 h<sup>-1</sup>) with very  
32 high selectivity for the desired products. On recycling, however, significantly lower  
33 activities were obtained due to severe Pd metal leaching (6.8% loss during reuse in  
34 the Heck reaction). However, TEM examination of the catalyst post reaction estab-  
35 lished the metal particles to preserve the original sizes with no sign of aggregation,  
36 clearly emphasizing the stabilizing effect of the ionic liquid on the catalyst material.

37 Supported catalyst materials containing metal particles have also been prepared by  
38 immobilizing ionic liquids in membrane materials. These systems have been tested  
39 for propene hydrogenation to propane in an asymmetric membrane arrangement  
40 [113, 114]. In the study, supported ionic liquid-polymer gel composite membrane  
41 materials composed of various air-stable ionic liquids, for example, [RMIM][X]  
42 (R = ethyl, butyl and X = [BF<sub>4</sub>]<sup>-</sup>, [PF<sub>6</sub>]<sup>-</sup>, [(CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>N]<sup>-</sup>), and poly(vinylidene  
43 fluoride)-hexafluoropropylene copolymers were prepared by the incorporation of a  
44 heterogeneous catalyst containing palladium metal (10 wt.%) on activated carbon.  
45 To accomplish the hydrogenation reactions, the ionic liquid membrane material

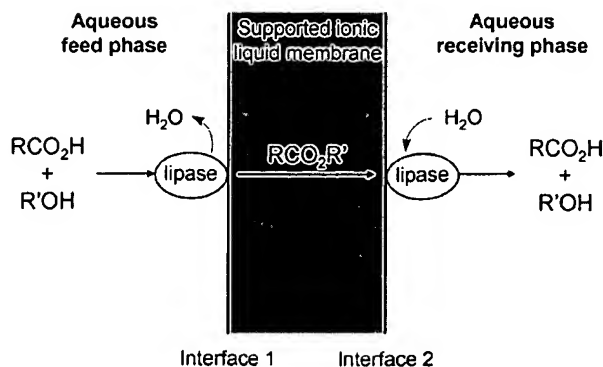


Fig. 5.6-11 Lipase facilitated separation of carboxylic acids using a supported ionic liquid membrane (modified from Ref. [118]).

was loaded into a membrane reactor set-up with the supported palladium metal particles on the permeate side of the membrane reactor. In this configuration, the palladium was activated by a hydrogen flow over the permeate side of the membrane, and the propene feed gas hydrogenated after it passed through the bulk of the membrane and reached the ionic liquid catalyst layer on the permeate side. Using  $[\text{EMIM}][(\text{CF}_3\text{SO}_2)_2\text{N}]$  as the catalyst phase a constant propene conversion of 73% could be achieved after 2 h of reaction.

#### 5.6.2.4.4 Supported ionic liquid catalytic membrane systems containing enzymes

Supported liquid membranes (SLM) containing ionic liquids have been used successfully for selective transport of e.g. alcohols, ketones, amines [115, 116] and aromatic hydrocarbons [117], according to the concentration gradient of the substance and its solubility in the ionic liquid.

Further development of the SLM-ionic liquid methodology has been coupled with lipase-catalyzed esterification and ester-hydrolysis reactions in the feed gas (interface 1) and receiving phase (interface 2), respectively, to facilitate selective transport of various organic acids with aryl groups (via their esters) from aqueous solutions by utilizing different substrate specificity of lipases in a SLM system (Fig. 5.6-11) [118]. In the enzymatic SLM systems a poly(propene) membrane with water-immiscible  $[\text{RMIM}][\text{X}]$  ( $\text{R}$  = butyl, hexyl, octyl and  $\text{X} = [\text{PF}_6]^-$  and  $[(\text{CF}_3\text{SO}_2)_2\text{N}]^-$ ) ionic liquid phases were used.

Using the same enzyme-SLM coupled principle as above, optical resolution of racemic ibuprofen (2-(4-isobutylphenyl)propionic acid) has also been achieved by utilizing the enantioselectivity of lipases for selective transport of (*S*)-ibuprofen [119]. For example, when using the poly(propene)/ $[\text{BMIM}][(\text{CF}_3\text{SO}_2)_2\text{N}]$  membrane system containing lipases originating from *Candida rugosa* and *Porsine pancreas* for esterification and hydrolysis in the feed gas phase and receiving phase, respectively, a maximum optical resolution ratio (i.e. ratio between initial permeate flux of (*S*)- and (*R*)-ibuprofen) of 3.9 and an enantiomeric excess (*ee*) of 75% of the (*S*)-isomer

## 554 | 5 Organic Synthesis

in the feed phase was obtained after 48 h of operation. In perspective, this result clearly demonstrates the potential for conducting enantioselective separations with enzyme-facilitated SLM systems based on ionic liquids.

## 5.6.3

## Concluding Remarks

This section summarizes the recent progress in supported ionic liquid catalysis, demonstrating synthetic applications where the ionic liquid can play its role as either “innocent” solvent (SILP) or the catalyst itself (SILC), depending on the specific cation/anion combination and the reaction under investigation.

Supported ionic liquid catalysis combines well-defined catalyst species, non-volatile ionic liquids, and porous solid supports in a manner which offers advantages over regular biphasic ionic liquid–organic liquid systems, e.g. substantially reduced amounts of catalyst and ionic liquid, higher turnovers, no loss of organic solvent and no catalyst leaching. Especially, the advantage of non-volatility of ionic liquids compared to traditional supported catalysts comprising organic solvents with low vapor pressure (SLP) or water (SAP) on supports, which are clearly limited by solvent evaporation, makes it possible to perform long-term stable, gas-phase, continuous processes using homogeneous, molecularly defined catalyst complexes in continuous fixed-bed reaction technology.

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## 5.7

### Multiphasic Catalysis Using Ionic Liquids in Combination with Compressed CO<sub>2</sub>

Peter Wasserscheid and Sven Kuhlmann

#### 5.7.1

##### Introduction

Ionic liquids are often considered as promising solvents for “clean processes” and “green chemistry” mainly due to their non-volatile character [1, 2]. These two catchwords represent current efforts to drastically reduce the amounts of side and coupling products, as well as the solvent and catalyst consumption in chemical processes. As another “green solvent” concept for chemical reactions the replacement of volatile organic solvents by supercritical CO<sub>2</sub> (scCO<sub>2</sub>) is frequently discussed [3]. scCO<sub>2</sub> combines an environmentally benign character (non-toxic, non-flammable) with favorable physicochemical properties for chemical synthesis. Catalyst

separation schemes have been developed on the basis of the tuneable phase behavior of  $scCO_2$  (CESS process) [4].

However, ionic liquids and  $scCO_2$  are not competing concepts for the same applications. While ionic liquids can be considered as replacements for polar organic solvents, the use of  $scCO_2$  can cover those applications where non-polar solvents are usually used.

With regard to homogeneous transition metal catalyzed reactions, both media show complementary strengths and weaknesses. While ionic liquids are known to be excellent solvents for many transition metal catalysts (see Section 5.3), the solubility of most transition metal complexes in  $scCO_2$  is poor. Usually, a special ligand design (e.g. phosphine ligands with fluororous "ponytails" [3]) is required to allow sufficient catalyst concentration in the supercritical medium. However, the product isolation from the solvent is always very easy in the case of  $scCO_2$ , while the product isolation from an ionic catalyst solution can become more and more complicated, depending on the solubility of the product in the ionic liquid and on the product's boiling point.

In cases where product solubility in the ionic liquid and the product's boiling point are high, the extraction of the product from the ionic liquid with an additional organic solvent is frequently proposed. This approach often suffers from some catalyst losses (due to small mutual solubility) and causes additional steps in the work-up. Moreover, the use of an additional, volatile extraction solvent may nullify the "green solvent" motivation to use ionic liquids as non-volatile solvents.

Beckman, Brennecke and their research groups first realized that the combination of  $scCO_2$  and an ionic liquid can offer special advantages. They observed that, although  $scCO_2$  is surprisingly soluble in some ionic liquids, the reverse is not the case, with no detectable ionic liquid solubilization in the  $CO_2$  phase. Based on these results they described a method to remove naphthalene quantitatively from the ionic liquid [BMIM][PF<sub>6</sub>] by extraction with  $scCO_2$  [5]. Subsequent work by Brennecke's team has applied the same procedure to extract a large variety of different solutes from ionic liquids, without observing any ionic liquid contamination in the isolated substances [6].

Research efforts aimed at quantifying the solubility of  $CO_2$  in ionic liquids revealed a significant influence of the ionic liquid's water content on the  $CO_2$  solubility. While water-saturated [BMIM][PF<sub>6</sub>] (up to 2.3 wt.% water) has a  $CO_2$  solubility of only 0.13 mol fraction, 0.54 mol fraction  $CO_2$  dissolves in dry [BMIM][PF<sub>6</sub>] (about 0.15 wt.% water) at 57 bar and 40 °C [7]. Kazarian et al. used ATR-IR to determine the  $CO_2$  solubility in [BMIM][PF<sub>6</sub>] and [BMIM][BF<sub>4</sub>]. They reported a solubility of 0.6 mol fraction  $CO_2$  in [BMIM][PF<sub>6</sub>] at 68 bar and 40 °C [8]. More recent research activities by Brennecke et al. have been directed towards the elucidation of the solvent strength [9] and the phase behavior of  $scCO_2$ /IL mixtures [10] and the determination of the solubility of various gases in ionic liquids. These studies have revealed that the solubility of  $CO_2$  in ionic liquids is mainly dependent on the anion structure. While [PF<sub>6</sub>] and [BF<sub>4</sub>]-based ILs show similar solubility, an increased solubility can be achieved using [BTA]-type ILs [11]. This behavior is largely independent of the cation structure.

The same authors also described the solubility of other gases such as oxygen, nitrous oxide, ethylene, ethane etc. in ionic liquids [12] and the beneficial influence of added CO<sub>2</sub> making oxygen and methane more soluble in ionic liquids [13]. Interestingly, Brennecke was able to show that oxygen solubility could be enhanced by a factor of 5.7 using [HMIM][BTA] and relatively low pressure (5.8 bar total pressure). Leitner and coworkers reported a dramatic increase in hydrogen solubility in the ionic liquid [EMIM][BTA] by pressurizing the ionic liquid with CO<sub>2</sub> [14].

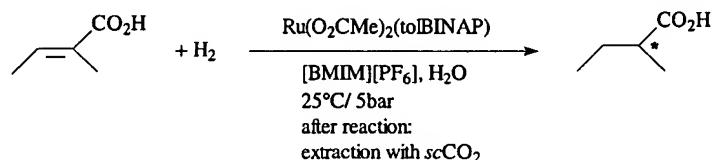
Other interesting and practically very relevant features of ionic liquid/scCO<sub>2</sub> biphasic systems have also been described. Han's group quantified for the first time the effect of compressed CO<sub>2</sub> on the viscosity of [BMIM][PF<sub>6</sub>]. They concluded that compressed CO<sub>2</sub> can indeed be effectively applied to reduce the viscosity of ionic liquids, e.g. to increase mass transfer rates. Similar effects were qualitatively observed before by other groups for many different ionic liquids. In addition, Leitner and Scurto reported very recently that the presence of compressed CO<sub>2</sub> leads to a very large melting point suppression of many ammonium and phosphonium salts [15]. Thus, a simple ammonium salt, such as [NBu<sub>4</sub>][BF<sub>4</sub>] (mp 156 °C) could be applied in catalytic reactions as an ionic liquid (melting point down to 55 °C) when the salt was contacted with 150 bar of CO<sub>2</sub>.

These publications demonstrate impressively that adding compressed CO<sub>2</sub> to an ionic liquid can significantly improve important physicochemical properties of the system. This offers a general tool to expand the application range of ionic liquids into more demanding process conditions.

### 5.7.2

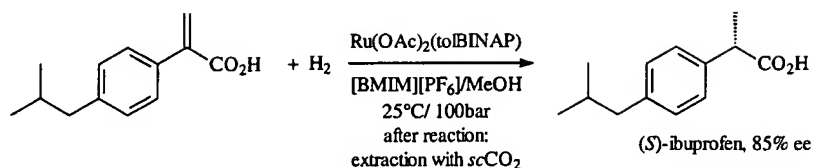
#### Catalytic Reaction with Subsequent Product Extraction

The first application including a catalytic reaction in an ionic liquid and a subsequent extraction step with scCO<sub>2</sub> was reported by Jessop et al. in 2001 [16]. They described two different, asymmetric hydrogenation reactions using [Ru(OAc)<sub>2</sub>(tolBINAP)] as the catalyst dissolved in the ionic liquid [BMIM][PF<sub>6</sub>]. In the asymmetric hydrogenation of tiglic acid (Scheme 5.7-1), the reaction was carried out in a [BMIM][PF<sub>6</sub>]/water biphasic mixture with excellent yield and selectivity. When the reaction was completed, the product was isolated by scCO<sub>2</sub> extraction without contamination by either catalyst or ionic liquid.



**Scheme 5.7-1** Asymmetric, Ru-catalyzed hydrogenation of tiglic acid in [BMIM][PF<sub>6</sub>] followed by extraction with scCO<sub>2</sub>.

## 560 | 5 Organic Synthesis



**Scheme 5.7-2** Synthesis of ibuprofen by asymmetric, Ru-catalyzed hydrogenation in [BMIM][PF<sub>6</sub>] with product isolation by subsequent extraction with scCO<sub>2</sub>.

Similarly, the asymmetric hydrogenation of isobutylatropic acid to the anti-inflammatory drug ibuprofen has been carried out (Scheme 5.7-2). Here, the reaction was carried out in a [BMIM][PF<sub>6</sub>]/MeOH mixture, again followed by a product extraction using scCO<sub>2</sub> (for more details on these hydrogenation reactions see Section 5.3).

Nunes da Ponte, Afonso and coworkers showed that asymmetric dihydroxylation of olefins could also be carried out successfully in [OMIM][PF<sub>6</sub>], leading to taxol fragments, which were reported to have antitumor activity [17]. Product recovery by extraction with diethyl ether as well as scCO<sub>2</sub> was attempted with the latter showing better yield and lower osmium content. In both cases recycling of the catalyst IL phase was achieved for six consecutive times without loss of activity. The same authors reported that the asymmetric Sharpless dihydroxylation could also be applied to various other substrates (e.g. 1-hexene, styrene etc.) using the above-mentioned technique [18].

### 5.7.3

#### Catalytic Reaction with Simultaneous Product Extraction

Baker, Tumas and coworkers reported catalytic hydrogenation reactions in a biphasic reaction mixture consisting of the ionic liquid [BMIM][PF<sub>6</sub>] and scCO<sub>2</sub> [19]. In the hydrogenation of 1-decene with Wilkinson's catalyst [RhCl(PPh<sub>3</sub>)<sub>3</sub>] at 50 °C and 48 bar H<sub>2</sub> (total pressure 207 bar) a conversion of 98% after 1 h was reported, corresponding to a turnover frequency (TOF) of 410 h<sup>-1</sup>. Under identical conditions the hydrogenation of cyclohexene proceeded with 82% conversion after 2 h (TOF = 220 h<sup>-1</sup>). The isolated ionic catalyst solution could be recycled in consecutive batch experiments up to four times. However, the fact that a biphasic hydrogenation of 1-decene can be successfully achieved is not a special benefit of the unconventional biphasic system [BMIM][PF<sub>6</sub>]/scCO<sub>2</sub>. In fact, no reactivity advantage with using scCO<sub>2</sub> in place of a more common alkane solvent for such a biphasic system can be concluded from the reported results.

Later, Ballivet-Tkatchanko and coworkers compared the palladium catalyzed dimerization of methyl acrylate in ionic liquids (monophasic) and IL/scCO<sub>2</sub> (biphasic) [20]. They found that both reactions exhibited similar selectivities for tail-to-tail dihydromuconate (>98%) as well as TOF/TON (95 h<sup>-1</sup> after 1 h/220 h<sup>-1</sup> after 3 h).

1 The latter was found to be a good indicator for the feasibility of a continuous mode  
2 of operation, as one might have expected a detrimental influence from the substrate  
3 being mainly dissolved in the CO<sub>2</sub> phase.

4 More recently, Leitner and coworkers studied the enantioselective hydrogenation  
5 of *N*-(1-phenylethylidene)aniline catalyzed by cationic iridium complexes with chiral  
6 phosphinooxazoline ligands in various ionic liquid/*sc*CO<sub>2</sub> systems [14]. They proved  
7 for this specific system a plethora of beneficial effects. While the presence of the  
8 *sc*CO<sub>2</sub> enabled the hydrogenation by high hydrogen availability (caused by both  
9 enhanced solubility and enhanced mass transfer rate due to lower ionic liquid  
10 viscosity), the presence of the ionic liquid led to an activation and stabilization  
11 of the cationic catalyst complex. Seven repetitive runs without significant catalyst  
12 deactivation could be realized.

#### 14 5.7.4

#### 15 Catalytic Conversion of CO<sub>2</sub> in an Ionic Liquid/*sc*CO<sub>2</sub> Biphasic Mixture

17 Parallel to their findings concerning hydrogenation in IL/*sc*CO<sub>2</sub> (see Section  
18 5.7.3), Baker, Tumas and coworkers also described the [RuCl<sub>2</sub>(dppe)]-catalysed  
19 (dppe=Ph<sub>2</sub>P-(CH<sub>2</sub>)<sub>2</sub>-PPh<sub>2</sub>) hydrogenation of CO<sub>2</sub> in the presence of dialkylamines  
20 to obtain *N,N*-dialkylformamides [19]. The reaction of di-*n*-propylamine in the sys-  
21 tem [BMIM][PF<sub>6</sub>]/*sc*CO<sub>2</sub> resulted in complete amine conversion, obtaining in high  
22 selectivity the desired *N,N*-di-*n*-propylformamide. The latter showed very high sol-  
23 ubility in the ionic liquid phase and complete product isolation by extraction with  
24 *sc*CO<sub>2</sub> proved to be difficult. However, product extraction with *sc*CO<sub>2</sub> became pos-  
25 sible once the ionic catalyst solution had become completely saturated with the  
26 product.

27 Other examples of CO<sub>2</sub> as a C1-building block include its reaction with propylene  
28 oxide as described by Kawanami and Ikushima [21]. They showed that the formation  
29 of cyclic carbonates in *sc*CO<sub>2</sub> and [OMIM][BF<sub>4</sub>] (the IL acts as the catalyst) can be  
30 achieved with various substrates in very high yield and selectivity (in some cases  
31 >99%) and up to 77 times faster than previously reported. Arai and coworkers have  
32 also demonstrated that epoxidation of olefinic substrates (i.e. styrene) with subse-  
33 quent formation of the cyclic carbonate could be carried out in a one-pot synthesis  
34 using IL/*sc*CO<sub>2</sub>. Yields of up to 33% could be achieved in tetrabutylammonium  
35 bromide with *tert*-butyl hydroperoxide as the oxidizing agent [22]. The same au-  
36 thors have also reviewed the feasibility of using *sc*CO<sub>2</sub> for the formation of cyclic  
37 carbonates [23].

#### 39 5.7.5

#### 41 Continuous Reactions in an Ionic Liquid/Compressed CO<sub>2</sub> System

43 Cole-Hamilton and coworkers demonstrated for the first time a flow apparatus for  
44 a continuous catalytic reaction using the biphasic system [BMIM][PF<sub>6</sub>]/*sc*CO<sub>2</sub> [24].  
45 They investigated the continuous Rh-catalyzed hydroformylation of 1-octene over

## 562 | 5 Organic Synthesis

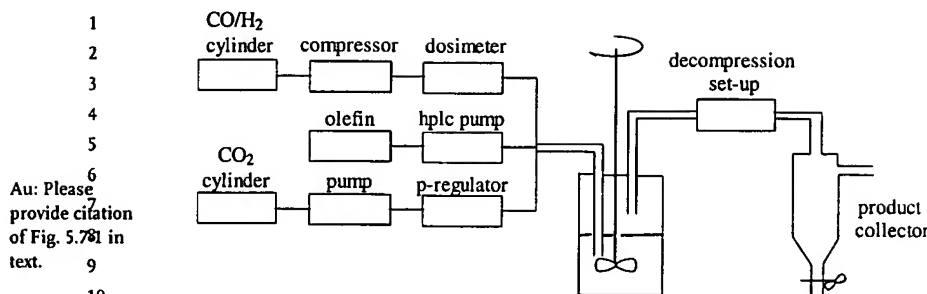


Fig. 5.7-1 Continuous flow apparatus as used for the hydroformylation of 1-octene in the biphasic system [BMIM][PF<sub>6</sub>]/scCO<sub>2</sub>.

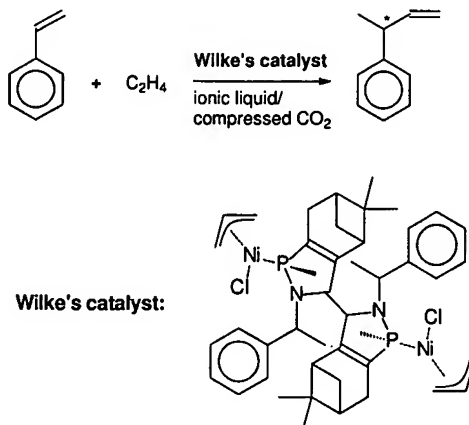
periods up to 33 h using the ionic phosphine ligand [PMIM]<sub>2</sub>[PhP(C<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>)<sub>2</sub>] ([PMIM] = 1-*n*-propyl-3-methylimidazolium). No catalyst decomposition was observed during the reaction time and Rh leaching into the scCO<sub>2</sub>/product stream was less than 1 ppm. The selectivity for the linear hydroformylation product was found to be stable over the reaction time (*n*/*iso* = 3.1).

During the continuous reaction, alkene, CO, H<sub>2</sub> and CO<sub>2</sub> were fed separately into the reactor which contained the ionic liquid catalyst solution. The products and non-converted feedstock were removed from the ionic liquid still dissolved in scCO<sub>2</sub>. After decompression, the liquid product was collected and analyzed.

Obviously, the motivation for performing this hydroformylation reaction in a continuous flow reactor arose from some problems during the catalyst recycling when the same reaction was first carried out in repetitive batch mode. In the latter case, Cole-Hamilton et al. observed a continuous drop of the product's *n*/*iso*-ratio from 3.7 to 2.5 over the first nine runs. Moreover, the isomerization activity of the system increased during the batchwise recycling experiments and after the ninth run Rh leaching became significant. From <sup>31</sup>P-NMR investigations the authors concluded that ligand oxidation due to contamination of the systems with air (during the reactor openings for recycling) led to the formation of [RhH(CO)<sub>4</sub>] as the active catalytic species. This is known to show more isomerization activity and lower *n*/*iso* ratio than the phosphine-modified catalyst system. Moreover, [RhH(CO)<sub>4</sub>] is more soluble in scCO<sub>2</sub>, which explains the observed leaching of rhodium into the organic layer.

All these problems related to the batchwise catalyst recycling could be convincingly overcome by applying the above described continuous operation mode. The authors concluded that the scCO<sub>2</sub>-ionic liquid biphasic system provides a method for continuous flow homogeneous catalysis with integrated separation of the products from the catalyst and from the reaction solvent. Most interestingly, this unusual, continuous biphasic reaction mode enables the quantitative separation of relatively high boiling products from the ionic catalyst solution under mild temperature conditions and without using an additional organic extraction solvent. More recently, Cole-Hamilton and coworkers were also able to show for the first time that





16 **Scheme 5.7-3** The enantioselective hydrovinylation of styrene using Wilke's catalyst.

17  
18  
19 high-boiling substrates (up to 1-dodecene) could be hydroformylated in a continu-  
20 ous operation using the methodology described above (IL = [BMIM][PF<sub>6</sub>]). In the  
21 corresponding aqueous biphasic catalysis, alkene chain-length is limited to C<sub>6</sub> by  
22 solubility and thus mass-transfer effects. The same phenomenon was observed in  
23 the IL/scCO<sub>2</sub> reaction mode (TOF = 5–10 h<sup>-1</sup> vs. 500–700 h<sup>-1</sup> for aqueous biphasic  
24 propene hydroformylation), but to a lesser extent. Moreover, by increasing the alkyl  
25 chain-length in the imidazolium cation [BMIM]<sup>+</sup> from butyl to octyl the reaction  
26 rate could be doubled, and by exchanging the [PF<sub>6</sub>]<sup>-</sup> anion to [BTA]<sup>-</sup> a further in-  
27 crease of more than 20% could be achieved. Thus, the conversion in the continuous  
28 reactor could be pushed to over 80% and, by adjusting the residence time, an opti-  
29 mized turnover frequency of up to 500 h<sup>-1</sup> could be achieved. Rhodium leaching is  
30 well below 1 ppm and the long-term stability of the catalyst could be proven over a  
31 period of 80 h [25].

32 Slightly later and independently from Cole-Hamilton's pioneering work, the au-  
33 thor's group demonstrated, in collaboration with Leitner et al., that the combination  
34 of a suitable ionic liquid and compressed CO<sub>2</sub> can offer much greater potential for  
35 homogeneous transition metal catalysis than being just a new protocol for easy prod-  
36 uct isolation and catalyst recycling. In the Ni-catalyzed hydrovinylation of styrene it  
37 was possible to activate, tune and immobilize the well-known Wilke complex by use  
38 of this unusual biphasic system (Scheme 5.7-3). Obviously, this reaction benefits  
39 from this special solvent combination in a new and highly promising manner.

40 Hydrovinylation is the transition metal catalyzed co-dimerization of alkenes with  
41 ethene yielding 3-substituted 1-butenes [26]. This powerful carbon–carbon bond  
42 forming reaction can be achieved with high enantioselectivity using Wilke's complex  
43 as a catalyst precursor [27]. In conventional solvents, this pre-catalyst needs to be  
44 activated with a chloride abstracting agent, e.g. Et<sub>3</sub>Al<sub>2</sub>Cl<sub>3</sub>. Leitner et al. reported the  
45 use of Wilke's complex in compressed CO<sub>2</sub> (under liquid and under supercritical

## 564 | 5 Organic Synthesis

conditions) after activation with alkali salts of weakly-coordinating anions such as Na[BARF] ( $[\text{BARF}]^- = \{(\text{3,5-}\text{CF}_3)_2\text{C}_6\text{H}_3)_4\text{B}\}^-$ ) [28].

At first, the reaction was investigated in batch mode using different ionic liquids with weakly coordinating anions as the catalyst medium and compressed  $\text{CO}_2$  as a simultaneous extraction solvent. These experiments revealed that the activation of Wilke's catalyst by the ionic liquid medium is obviously very dependent on the nature of the ionic liquid's anion. Comparison of the results in different ionic liquids with [EMIM] $^+$  as the common cation showed that the catalyst's activity decreases in the order  $[\text{BARF}]^- > [\text{Al}\{\text{OC}(\text{CF}_3)_2\text{Ph}\}_4\}^- > [(\text{CF}_3\text{SO}_2)_2\text{N}]^- > [\text{BF}_4]^-$ . This trend is consistent with the estimated nucleophilicity/coordination strength of the anions.

Interestingly, the specific environment of the ionic solvent system appears to activate the chiral Ni catalyst beyond a simple anion exchange reaction. This becomes obvious by the fact that even the addition of a 100-fold excess of  $\text{Li}[(\text{CF}_3\text{SO}_2)_2\text{N}]$  or  $\text{Na}[\text{BF}_4]$  in pure, compressed  $\text{CO}_2$  lead at best to a moderate activation of Wilke's complex in comparison to the reaction in ionic liquids with the corresponding counter ion (e.g. 24.4% styrene conversion with 100-fold excess of  $\text{Li}[(\text{CF}_3\text{SO}_2)_2\text{N}]$  in comparison to 69.9% conversion in [EMIM] $[(\text{CF}_3\text{SO}_2)_2\text{N}]$  under otherwise identical conditions).

In the biphasic batch reaction the best reaction conditions were assessed for the system [EMIM] $[(\text{CF}_3\text{SO}_2)_2\text{N}]$ /compressed  $\text{CO}_2$ . It was found that increasing the partial pressure of ethylene and decreasing the temperature helped to suppress the concurrent side reactions (isomerization and oligomerization). 58% conversion of styrene (styrene/Ni = 1000/1) was achieved after 1 h under 40 bar of ethylene at 0 °C whereby 3-phenyl-1-butene was detected as the only product with 71% ee of the (R)-isomer.

However, attempts to reuse the ionic catalyst solution in consecutive batch experiments failed. While the products could be readily isolated after reaction by extraction with  $\text{scCO}_2$ , the active nickel species deactivated rapidly within three to four batchwise cycles. The fact that no such deactivation was observed in later experiments using the continuous flow apparatus described below (see Fig. 5.7-2) clearly indicates the deactivation of the chiral Ni catalyst being mainly related to the instability of the active species in the absence of substrate.

In the continuous hydrovinylation experiments, the ionic catalyst solution was placed into the reactor R where it was in intimate contact with the continuous reaction phase entering from the bottom (no stirring was used in these experiments). The reaction phase was made up in the mixer from a pulsed flow of ethylene and a continuous flow of styrene and compressed  $\text{CO}_2$ .

Figure 5.7-3 shows the results of a lifetime study for Wilke's catalyst dissolved, activated and immobilized in the system [EMIM] $[(\text{CF}_3\text{SO}_2)_2\text{N}]$ /compressed  $\text{CO}_2$ . Over a period of over 61 h, the active catalyst showed a remarkably stable activity while the enantioselectivity dropped only slightly over this period. These results clearly indicate – at least for the hydrovinylation of styrene with Wilke's catalyst – that an ionic liquid catalyst solution can show excellent catalytic performance under continuous product extraction with compressed  $\text{CO}_2$ .

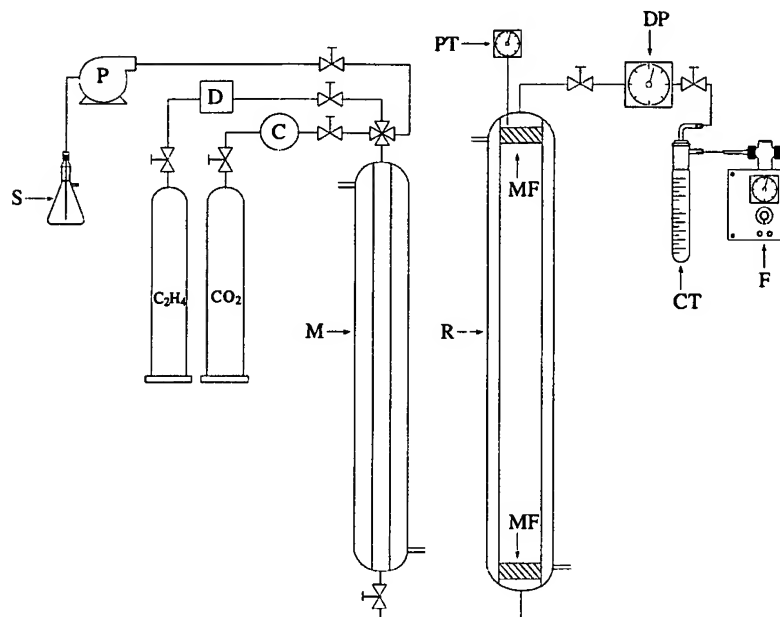
5.7 Multiphase Catalysis Using Ionic Liquids in Combination with Compressed CO<sub>2</sub> | 565

Fig. 5.7-2 Schematic view of the continuous flow apparatus used for the enantioselective hydrovinylation of styrene in the biphasic system [EMIM][(CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>N]. The parts are labeled as follows (alphabetically): C, Compressor; CT, cold trap; D, dosimeter; DP, depressurizer; F, flowmeter; M, mixer; MF, metal filter; P, HPLC pump; PT, pressure transducer and thermocouple; R, reactor; S, styrene.

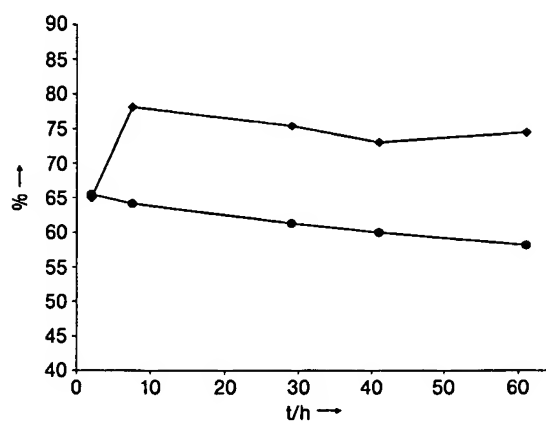


Fig. 5.7-3 Lifetime study of Wilke's catalyst in the hydrovinylation of styrene activated and immobilized in the system [EMIM][(CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>N]/compressed CO<sub>2</sub> (● ee; ◇ conversion).

In the context of continuous-flow operations using  $scCO_2$ /ILs, it has to be mentioned that this concept has also been successfully applied to biocatalyzed reactions. Among others, Reetz et al. were able to demonstrate that kinetic resolution of alcohols is possible by lipase-catalyzed alcohol esterification in ILs and subsequent continuous extraction of the ester derivatives with  $scCO_2$  [29]. For further information, see Chapter 8.

#### 5.7.6

#### Concluding Remarks and Outlook

The combination of ionic liquids and compressed  $CO_2$  – which are on the extreme ends of the volatility and polarity scale – offers a new intriguing immobilization technique for homogeneous catalysis.

In comparison to catalytic reactions in compressed  $CO_2$  alone, many transition metal complexes are much more soluble in ionic liquids without the need for special ligands. Moreover, the ionic liquid catalyst phase provides the potential to activate and tune the organometallic catalyst. Furthermore, product separation from the catalyst is now possible without exposing the catalyst to a variation of temperature, pressure or substrate concentration.

In contrast to the use of pure ionic liquid, the presence of compressed  $CO_2$  greatly decreases the viscosity of the ionic catalyst solution, thus facilitating mass transfer during the catalytic reaction. Moreover, high boiling products with some solubility in the ionic liquid phase can now be removed without the use of an additional organic solvent. Finally, the use of compressed  $CO_2$  as the mobile phase enables the use of a reactor design that is very similar to a classical fixed bed reactor [30]. Thus, the combination of ionic liquids and compressed  $CO_2$  provides a new highly attractive approach that benefits from the advantages of both homogeneous and heterogeneous catalysis. Moreover, this approach promises to overcome some of the well-known limitations of conventional biphasic catalysis (catalyst immobilization, feedstock solubility in the catalytic phase, solvent cross-contamination, mass transfer limitation). In particular, the combination of non-volatile ionic liquids with non-hazardous  $CO_2$  offers fascinating new possibilities to design environmentally benign processes.

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# Ionic Liquid Droplet as e-Microreactor

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A powerful approach combining a droplet-based, open digital microfluidic lab-on-a-chip using task-specific ionic liquids as soluble supports to perform solution-phase synthesis is reported as a new tool for chemical applications. The negligible volatility of ionic liquids enables their use as stable droplet reactors on a chip surface under air. The concept was validated with different ionic liquids and with a multicomponent reaction. Indeed, we showed that different ionic liquids can be moved by electrowetting on dielectric (EWOD), and their displacement was compared with aqueous solutions. Furthermore, we showed that mixing ionic liquids droplets, each containing a different reagent, in "open" systems is an efficient way of carrying supported organic synthesis. This was applied to Grieco's tetrahydroquinolines synthesis with different reagents. Analysis of the final product was performed off-line and on-line, and the results were compared with those obtained in a conventional reaction flask. This technology opens the way to easy synthesis of minute amounts of compounds ad libitum without the use of complex, expensive, and bulky robots and allows complete automation of the process for embedded chemistry in a portable device. It offers several advantages, including simplicity of use, flexibility, and scalability, and appears to be complementary to conventional microfluidic lab-on-a-chip devices usually based on continuous-flow in microchannels.

In recent years, lab-on-a-chip systems dedicated to biotechnological and chemical applications have attracted growing interest.<sup>1–6</sup> Compared to traditional batch reaction, miniaturized systems allow the use of very small quantities of reagents while optimizing the

reactions and producing the desired products faster and in greater yield and purity. However, these microsystems, usually consisting of a network of micrometer-sized channels embedded into a solid substrate, suffer from several drawbacks, such as large dead volumes or frequent obstruction of the channels. Moreover, in continuous flow microfluidic systems, constant hydrodynamic pressure can be difficult to maintain (especially for viscous liquids), or surface charges are hard to control (when an electroosmotic pumping is used). In an attempt to avoid these problems, Zheng and Ismagilov<sup>7</sup> have described a continuous flow microfluidic system in which droplets are separated by liquid spacers, but complex protocols are relatively difficult to perform with this system. To overcome all these difficulties, it has been proposed<sup>8,9</sup> that droplet microreactors containing reagents, samples, etc., could be displaced on two-dimensional chips (as opposed to microfluidic channels) by various fluidic actuators, such as acoustic waves or, more often, electrowetting on dielectric (EWOD). Those droplet microfluidic systems have several advantages, such as complex fluidic connections and associated problems (as previously described) can be avoided. Furthermore, this so-called digital<sup>10</sup> approach gives great flexibility in the creation and handling of droplet microreactors. We, thus, decided to use this technology in our attempt to create a chemical microprocessor.

Most of the applications reported so far, however, are biological reactions, such as PCR (polymerase chain reaction),<sup>11,12</sup> and are performed in aqueous solvents, which are often not suitable for chemical synthesis. Only recent works have described the use of organic solvents in such systems.<sup>13</sup> Furthermore, volatile organic solvent (VOS) droplets evaporate very rapidly in open microsystems due to their high volatility. On the other hand, manipulating VOS droplets in closed microsystems or under oil would introduce other problems, such as complications in the fluidic connections (comparable to microchannel systems), cross-contaminations, and oil/solvent miscibility. Using digital microfluidic "open" systems

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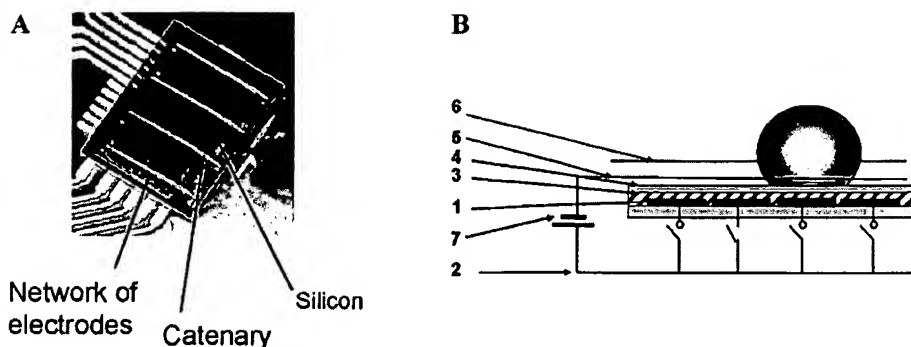
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**Figure 1.** (A) Picture of the chip (10 mm  $\times$  7 mm). (B) Schematic representation of the chip. Each electrode (1) ((800  $\mu\text{m}^2$ ), of the matrix is electrically connected to a conducting layer (2). The electrodes (1) were covered with an insulating (3) and hydrophobic (4) layer. The chip has a first catenary (25- $\mu\text{m}$  diameter) (5), essential for the electrowetting, and a second (6), allowing two electrodes for electrochemical measurements. A generator (7) is connected to the electrodes.

(with no coverage) has several advantages from a technological point of view, as we recently suggested.<sup>14</sup> We therefore decided to use ionic liquids (ILs) in our chemical microprocessor, assuming that these particular solvents could be used in open microsystems without evaporating.

Ionic liquids have recently attracted considerable attention. Some of them, the so-called room temperature ionic liquids (RTILs), are free-flowing liquids at room temperature. Due to their negligible vapor pressure, they are considered “greener” alternatives to VOSs. Numerous applications of RTILs as nonaqueous polar alternatives in biphasic systems, as extraction solvents,<sup>15</sup> or as electrolytes<sup>16,17</sup> have been reported. They are also used in organic synthesis<sup>18–21</sup> and organometallic or enzymatic<sup>22</sup> catalysis. Moreover, a unique subclass of ionic liquids, task-specific ionic liquids (TSILs) have greatly widened the utilization scope of ionic liquids.<sup>23–27</sup> Their functional groups, covalently linked to the cation, the anion, or both, confer additional properties to these salts, thereby expanding their potential applications far beyond those of conventional ionic liquids. Moreover, TSILs and RTILs can be combined in solutions. Hence, supported synthesis in a homogeneous solution can be achieved, which is a major advantage.<sup>28,29</sup>

Recent works have explored the behavior of some RTILs in electrowetting,<sup>13,30</sup> but the authors did not describe associated applications. In our study, we have explored the possibility of using droplets of RTILs and TSILs as stable microreactors on an open digital microfluidic chip<sup>11</sup> using electrowetting on dielectric as the fluidic actuator. This rapidly appeared to be a very promising approach for low-volume organic synthesis in solution. The very low evaporation rate of ionic liquids allows handling of very small volume droplets without cover or oil, thus simplifying the experiments, facilitating direct access to the droplets, and avoiding possible cross-contaminations within the oil layer between droplets. Furthermore, complex protocols can be achieved on such a system due to the easy displacement of droplets by EWOD. In this paper, we describe our results, showing the specific behavior of ionic liquids when subjected to EWOD actuation, and the use of this powerful technology for the easy handling of reagents and efficient completion and monitoring of a multicomponent reaction.

## EXPERIMENTAL SECTION

**Description of the Chip.** In our system, as shown in Figure 1, the chip consists of a network of gold electrodes structured on silicon: a dielectric layer to avoid electrochemical reactions during the actuation of electrodes; a hydrophobic layer, necessary to obtain a contact angle compatible with electrowetting; and a gold microcatenary, which enables the polarization of the droplet and its guidance during displacement. These experiments were performed under air in an “open” microsystem. A second catenary that allows electrochemical measurements between the first and the second catenaries can be added. To generate droplets from a reservoir (“closed” microsystem), the first catenary can be replaced by a plate recovered with a metallic transparent layer (indium tin oxide) and a Teflon layer.

**Fabrication of the Device.** In this technology, one wafer of silicon and one microstructured metal layer are needed. After performing wet oxidation (2  $\mu\text{m}$ ) on the wafer, the gold electrodes ((800  $\mu\text{m}^2$ ) were formed by deposition of a 5-nm layer of Cr and then 300 nm of Au on the wafer, followed by patterning using standard microfabrication techniques. Next, the wafer was coated with a 300-nm layer of silicon nitride ( $\epsilon_r = 7.8$ ) deposited by PECVD followed by an etching of this layer for electrical contact.

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After sawing off the wafer, an  $\sim 1\text{-}\mu\text{m}$  spin-coated layer of amorphous Teflon-AF-1601 of DuPont ( $\epsilon_{\text{R}} = 1.9$ ) was deposited on the chips.

**Packaging of Chips.** The chips ( $10\text{ mm} \times 7\text{ mm}$ ) were glued on a PCB support and connected by wire bonding (gold wires,  $25\text{ }\mu\text{m}$ ). The wire bonding machine was also used to create a network of thin metallic catenaries ( $25\text{ }\mu\text{m}$ ) over the chip, required for EWOD actuation.

**Electrowetting Curves.** The contact angle of a  $1\text{-}\mu\text{L}$  droplet on the surface was measured with a commercial apparatus (Digidrop from GBX) with an image software using the drop profile method. The software calculates the contact angle from the fit of the drop shape. The voltage was supplied by an AC voltage generator. The frequency was fixed at  $3\text{ kHz}$ . The generator delivers an efficient variable output of  $0$  to  $90\text{ V (rms)}$ .

**Instrumentation.** The packaged chip was connected to electrical switches driven by a computer that can activate the different electrodes and control the displacement of droplets.

Voltammetric measurements for detection were performed on a chip connected to an EGG-PAR model 283 potentiostat equipped with Echem software.

**Reagents.** Indene, 4-nitroaniline, 4-bromoaniline, aniline, 4-bromobenzaldehyde, 4-nitrobenzaldehyde, and trifluoroacetic acid were purchased through Aldrich-Sigma and used without further purification.

**Ionic Liquids Preparation.** 1-Butyl-3-methylimidazolium tetrafluoroborate [bmim][BF<sub>4</sub>] (**B**) and 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF<sub>6</sub>] (**C**) are commercially available (Merck KGaA) and were used without further purification. The other ionic liquids were synthesized according to protocols established in the laboratory and described in the Supporting Information.

**Grieco's Reaction. Synthesis of [3-(4-formylbenzoyloxy)-propyl]-trimethylammonium tetrafluoroborate 1.** In a sealed flask, to one equiv of 1-chloropropan-3-ol was added 2 equiv of trimethylamine (45 wt % aqueous solution) and the minimum volume of acetonitrile to obtain a monophasic reaction medium. The flask was heated to  $70\text{ }^{\circ}\text{C}$  overnight. After elimination of volatiles and solvents under vacuum, the residue was washed with diethyl ether and recrystallized from acetone, leading to a white solid. To 1 equiv of 3-hydroxypropyltrimethylammonium chloride dissolved in acetonitrile were added 1.5 equiv of *N,N'*-dicyclohexylcarbodiimide, 1.5 equiv of 4-carboxybenzaldehyde, and 0.02 equiv of 4-(dimethylamino)pyridine. The reaction was carried out in a flask at room temperature for 4 h. Solvents were removed by vacuum distillation, and the ester created was removed by washing with water. A 1.5-equiv portion of HBF<sub>4</sub> (50% water solution) was added to the previous ester and mixed for 2 h at room temperature. After filtration and evaporation of water, product **1** was obtained as a white solid. Yield: 90%. <sup>1</sup>H NMR (200 MHz, CD<sub>3</sub>CN)  $\delta$ : 2.10–2.33 (m, 2H), 3.05 (s, 9H), 3.36–3.55 (m, 2H), 4.45 (t, 2H,  $J = 5.8\text{ Hz}$ ), 8.00 (dd, 2H,  $J_1 = 1.6\text{ Hz}$ ,  $J_2 = 6.6\text{ Hz}$ ), 8.13 (dd, 2H,  $J_1 = 1.4\text{ Hz}$ ,  $J_2 = 8.3\text{ Hz}$ ), 10.10 (s, 1H). <sup>13</sup>C NMR (50 MHz, CD<sub>3</sub>CN)  $\delta$ : 22.08, 52.66 (t,  $J = 3.8\text{ Hz}$ ), 61.53, 63.52 (t,  $J = 3.0\text{ Hz}$ ), 129.10, 129.80, 134.39, 139.27, 164.89, 192.04. ESI-MS for C<sup>+</sup>: calcd, 250.3; found, 250.2.

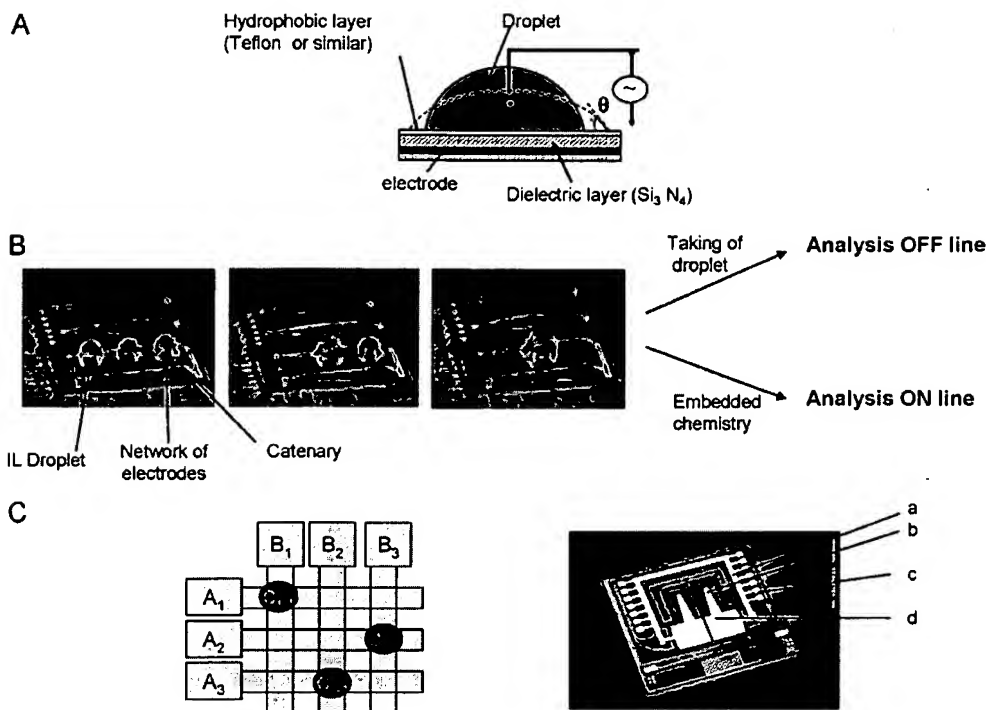
**Synthesis of 3-[4-(4-aminobenzoyloxy)-propyl]-trimethylammonium Bis(trifluoromethylsulfonyl)imide 5.** To 1 equiv of 3-hydroxypro-

pyltrimethylammonium chloride (see synthesis above) dissolved in acetonitrile were added 1.5 equiv of *N,N'*-dicyclohexylcarbodiimide, 1.5 equiv of 4-nitrobenzoic acid, and 0.02 equiv of 4-(dimethylamino)pyridine. The reaction was carried out in a flask at room temperature for 4 h. Solvents were removed by vacuum distillation, and the ester created was removed by washing with water. Afterward, the reduction of the nitro group was performed by the addition of 0.01 equiv of Pd/C and stirring at room temperature under 5 bar pressure of hydrogen for 48 h. The metathesis was performed by adding 1.1 equiv of bis(trifluoromethylsulfonyl)imide lithium dissolved in the minimum of water. After 2 h of stirring at room temperature, water was eliminated, and the solution was washed with diethyl ether. After filtration and evaporation of water, product **5** was obtained as a white solid. Yield: 93%. <sup>1</sup>H NMR (200 MHz, acetone-*d*<sub>6</sub>)  $\delta$ : 2.35–2.54 (m, 2H), 3.41 (s, 9H), 3.78–3.92 (m, 2H), 4.5 (t, 2H), 5.51 (s, 2H), 6.58 (d, 2H), 7.84 (d, 2H). <sup>13</sup>C NMR (50.32 MHz, acetone *d*<sub>6</sub>)  $\delta$ : 24.17, 54.12 (t,  $J_{\text{C-N}} = 4.1\text{ Hz}$ ), 61.72, 65.60, 114.25, 118.33, 121.17 (q,  $J_{\text{C-F}} = 320.9\text{ Hz}$ ), 132.72, 154.74, 167.08. HRMS (FAB) for (2C<sup>+</sup>, NTf<sub>2</sub>)<sup>+</sup>: calcd, 754.2379; found 754.2379.

**Synthesis of the Internal Reference M.** In a seal flask, to 1 equiv of 3-hydroxypropyltrimethylammonium chloride (see synthesis above) dissolved in acetonitrile was added 1.2 equiv of bis(trifluoromethylsulfonyl)imide lithium dissolved in the minimum of water. After 2 h of stirring at room temperature, water was eliminated, and the solution was washed with diethyl ether. To 1 equiv of this alcohol dissolved in acetonitrile 1.1 equiv of dansyl chloride dissolved in CH<sub>2</sub>Cl<sub>2</sub> and 1.2 equiv of K<sub>2</sub>CO<sub>3</sub> was added, and the mixture was mixed 36 h at room temperature. After evaporation of organic solvents, the mixture was washed with diethyl ether and then with water. The internal reference (yellow solid) was obtained after vacuum evaporation of residual solvents. Yield = 10%. <sup>1</sup>H NMR (200 MHz, acetone-*d*<sub>6</sub>)  $\delta$ : 2.35 (m, 2H), 2.93 (s, 6H), 3.37 (s, 9H), 3.64 (m, 2H), 4.21 (t, 2H), 7.35 (d, 1H), 7.65–7.8 (q, 2H), 8.2–8.35 (q, 2H), 8.72 (d, 1H). <sup>13</sup>C NMR (200 MHz, acetone-*d*<sub>6</sub>)  $\delta$ : 23.03, 45.00, 53.10 ( $J_{\text{C-N}} = 4.1\text{ Hz}$ ), 63.5, 67.8, 116.1, 117.1, 119.2, 123.8, 129.2, 129.8, 131.0, 131.2, 132.0. ESI-MS for C<sup>+</sup>: calcd, 351.17; found, 351.27.

**Reaction in Droplets.** Three solutions were prepared: solution A, a 0.20 M solution of **1** or **5** dissolved by heating in [tmbsa]-[NTf<sub>2</sub>] (1 equiv); solution B, a 0.5 M solution of the respective aniline (**2a**, **2b**, or **2c**) or benzaldehyde (**6a** or **6b**); and solution C, a 2 M solution of indene **3** (10 equiv) in the same solvent as **1**. The TFA (10 equiv) was added in solution A with **1** or in solution B with **5**. To determine the conversion rate, the internal reference, **M**, was added at a concentration of 0.02 M in solution A. Drops of  $0.3\text{ }\mu\text{L}$  of solutions A, B, and C were deposited on the chip using an Eppendorf micropipet. The drops were merged successively. All displacement and merging were performed with a tension of 55 V rms. The actuation of electrodes was switched, and the reaction was carried out at room temperature for 1 h. After incubation, either the droplet was analyzed by electrochemical detection or it was taken off with a micropipet and the reaction was quenched by washing with a large excess of diethyl ether. Residual ether was removed under vacuum. Samples were diluted in  $50\text{ }\mu\text{L}$  of a 1:1 mixture of acetonitrile/water, and  $10\text{ }\mu\text{L}$  of each was injected into the HPLC. Samples were analyzed using a column Supelcosil C18 LC-318 on a Waters Alliance 2695 HPLC





**Figure 2.** (A) Principle of electrowetting on dielectric (EWOD). The contact angle ( $\theta$ ) of the droplet is modified when a voltage is applied between the surface and the catenary. (B) Chemical synthesis mechanism on an e-microreactor (see Experimental Section) followed by the off-line or on-line analysis of the final product. An ionic liquid droplet containing a given reagent is moved on the chip by EWOD and merged with the other ionic liquid droplets containing the other reagents. (C) Left: design of a multiplexed chip<sup>8</sup> that would allow performing synthesis in parallel. Right: example of a complex fluidic processor<sup>12</sup> (26 mm  $\times$  21 mm) designed for parallel syntheses. (a) Electrode bus for fluidic communication (1 mm<sup>2</sup> for each electrode), (b) reservoir entry, (c) reagent storage and dispensing (volume, 1–3  $\mu$ L), and (d) reservoir for TSIL dispensing (volume, 100 nL).

and Waters UV detector 2487 at 254 nm. The rest of the samples were diluted in 1 mL of a 1:1 mixture of acetonitrile/water and analyzed by ESI-MS in a Thermo LTQ with glass picotip. Electrospray ionization was carried out in the positive mode at an ionization potential of 1300 V. Scans were recorded at 20 scans/min.

## RESULTS AND DISCUSSION

**Principle of the System.** The electronic microreactor (e-microreactor, Figure 2) described in this paper is an “open” digital microfluidic chip on which electrowetting on dielectric (EWOD) actuation is used to displace ionic liquid droplets.

Electrowetting on dielectric is an actuation mechanism used for conducting liquids; it is based on the principle of controlling the surface's wettability by applying a voltage. EWOD actuation thus allows moving and merging ionic liquid droplets (microreactors) containing different reagents in a very flexible way. Moreover, the negligible vapor pressure of ionic liquids allows handling very small liquid volumes (<1  $\mu$ L) on open microsystems. Chemical syntheses with minute amounts of reagents (especially useful for potentially explosive or expensive reactions) are, therefore, made possible. The reactions can be achieved in solution using ionic liquid matrixes, such as RTILs. Moreover, supported chemistry could be achieved on soluble supports, such as TSILs. In this case, the excess of reagents and byproducts could be eliminated at the end of the reaction by simply washing or heating the droplets. The final product can be analyzed either by an external detection system, such as mass spectrometry or by

HPLC (off-line analysis), or directly on the chip, that is, by electrochemical measurement, as discussed in this article (on-line analysis). The latter opens the way to complete automation of the synthesis process for completely integrated (embedded) chemistry on a portable device.

Finally, the simplicity and flexibility of EWOD actuation combined with the possibility of multiplexing<sup>8,10,31</sup> reactions on two-dimensional chips offer the opportunity to design powerful tools for high-throughput combinatorial synthesis of organic compounds, protocol optimization, or multistep synthesis, as shown in Figure 2C.

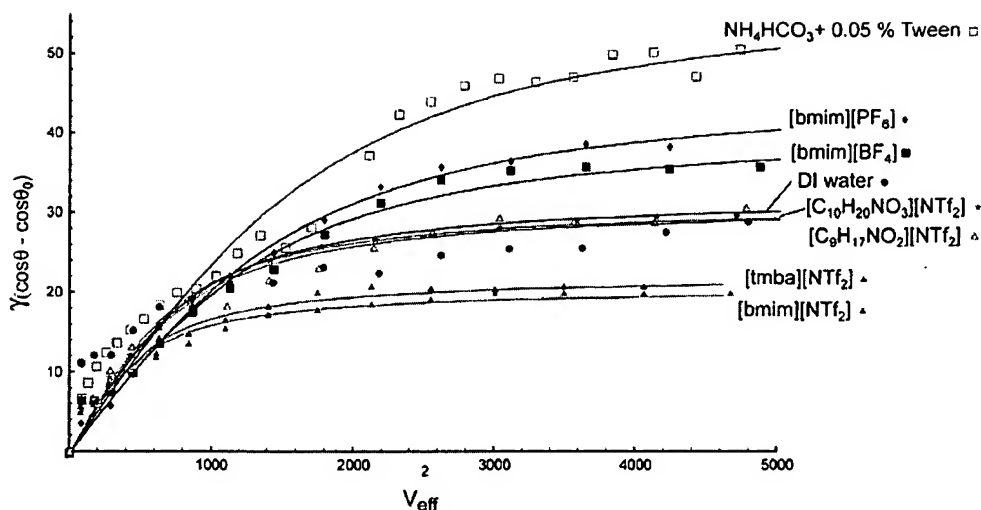
**Constitutive Law of Ionic Liquids under EWOD Actuation.** The EWOD technology is based on the observation that an electrical field modifies the contact angle of a conducting droplet on a hydrophobic substrate<sup>11</sup> (Figure 2A). This principle is described by the Lippmann–Young equation (eq 1) and was first reported by Berge,<sup>32</sup>

$$\cos \theta = \cos \theta_0 + \frac{1}{2} \frac{C}{\gamma_{LG}} V^2 \quad (1)$$

where  $\theta_0$  is the natural contact angle,  $\theta$  is the contact angle when the electric field is actuated,  $C$  is the capacitance per surface unit of the layer between the electrodes and the liquid,  $V$  is the applied

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**Figure 3.** Langevin's function for the  $\text{NH}_4\text{HCO}_3$  25mM + 0.05% Tween 20 buffer, deionized water, and various ionic liquids. Contact angles were measured on 1- $\mu\text{L}$  droplets.

voltage, and  $\gamma_{\text{LG}}$  is the surface tension between the drop and the surrounding fluid (air or insulating liquid).

In Figure 3, a plot of the values of  $\gamma (\cos \theta - \cos \theta_0)$  versus  $V^2$  on a Teflon-coated chip under air for different ionic liquids, a biological buffer containing 0.05% Tween 20, and deionized water (DI water) is reported. As recently reported by Millefiori et al.,<sup>30</sup> we confirmed that the electrowetting of ionic liquids is less efficient than aqueous salt solutions. On the other hand, the comparison of electrowetting curves of DI water and ionic liquids showed that, in function of ionic liquids, the efficiency of the electrowetting is higher or lower than or similar to water.

Note that the same cation  $\text{bmim}^+$  with three different anions leads to three different behaviors. Indeed, the maximum saturation is reached for  $[\text{bmim}][\text{PF}_6]$ , whereas the minimum is obtained with  $[\text{bmim}][\text{NTf}_2]$ . On the other hand, for the same anion  $\text{NTf}_2^-$  with four different cations, only two distinct behaviors were observed. This could be explained by, on one hand, the relatively closed structures of the cations  $\text{bmim}^+$  and  $\text{tmba}^+$  and, on the other hand, the strong similarity of structure between the cations  $\text{C}_{10}\text{H}_{20}\text{NO}_3^+$  and  $\text{C}_9\text{H}_{17}\text{NO}_2^+$  (see Supporting Information). Thus, we suggest that both the anion and the cation have an influence on the electrowetting curves. However, as well-established, we showed that the Lippmann–Young relation is only valid at low voltage. Indeed, the experimental curves are linear at low voltages (with a coefficient equal to  $C/2\gamma$ ), whereas a saturation threshold, of which the origin is completely unclear at high voltage, was observed.<sup>33</sup>

It has recently been observed that the Langevin equation (eq 2) models well the experimental values of biological buffer with surfactants.<sup>34</sup>

$$L(X) = \coth(3X) - \frac{1}{3X} \quad (2)$$

Thus, we obtained the following equation (eq 3).

$$\frac{\cos \theta - \cos \theta_0}{\cos \theta_s - \cos \theta_0} = L\left(\frac{CV^2}{2\gamma(\cos \theta_s - \cos \theta_0)}\right) \quad (3)$$

In Figure 3, the calculated curve (Langevin's function) and our experimental data for biological buffers with surfactants, DI water, and ionic liquids have been superimposed. We thus observed that the Langevin's function could be used to fit empirically the electrowetting curves. Thus, it appears that, similar to biological buffers and water, ionic liquids follow the same extended Lippmann–Young law. Therefore, ILs, biological buffers, and water are ruled by the same constitutive law; however, we should note that for water and for the biological buffer, the experimental points do not fit perfectly with the Langevin function. This fact is certainly due to the evaporation of those solutions, whereas for ionic liquids, which are not sensitive to evaporation, data points fit well with Langevin function, except for the first two or three points (this fact is not fully understood yet).

Finally, an estimation of the hysteresis for different RTILs on Teflon under air was performed from the advancing and receding angles on electrowetting curves. Thus, values around 2–3° for  $[\text{tmba}][\text{NTf}_2]$ ,  $[\text{bmim}][\text{NTf}_2]$ , and  $[\text{C}_{10}\text{H}_{20}\text{NO}_3][\text{NTf}_2]$ ; around 7° for  $[\text{bmim}][\text{BF}_4]$ ; and 8° for  $[\text{bmim}][\text{PF}_6]$  were determined. Moreover, the hysteresis seems to depend on the nature of the anion.

**Motion of Ionic Liquids.** As shown in Table 1, ionic liquids demonstrated particular behaviors on a hydrophobic surface under air, as compared to water. These particular behaviors are smaller contact angles ( $\theta_0 = 70$ – $94^\circ$  for ILs versus  $110^\circ$  for water) and low surface tensions (34–46 mN/m for RTILs versus 72 mN/m for water). An addition of 1% Tween 20 to water was necessary to obtain contact angles and surface tensions close to ionic liquids values. Furthermore, their contact angle at saturation ( $\theta_s$ ) is smaller than water. It is also important to notice that the studied ILs exhibit very high viscosity values ( $\eta$ ), between 80 and 300 cP, as compared to 0.89 cP for water, at 25 °C.<sup>35</sup>

As a result of these differences, different dynamic behaviors of aqueous solutions, as compared to ionic liquids, were expected.

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**Table 1. Physical Characteristics of Ionic Liquids in Comparison with Water<sup>a</sup>**

ionic liquids	$\gamma^b$	$\theta_0^c$	$\theta_S^d$	$V_{\min}^e$	$V_{\max}^f$	$\rho^g$	$\nu^h$
[tmba][NTf <sub>2</sub> ] A	34.5	77	30–45	18 ± 1	48 ± 2	1.43	57
[bmim][BF <sub>4</sub> ] B	46.3	94.2	40–45	22 ± 3	58 ± 2	1.17	103.7
[bmim][PF <sub>6</sub> ] C	43.6	94.8	30–40	26 ± 1	58 ± 2	1.37	223.7
[bmim][NTf <sub>2</sub> ] D	33.9	76.5	30–35	18 ± 2	53 ± 3	1.43	
[teba][NTf <sub>2</sub> ] E		76.5	30–32	18 ± 2	48 ± 3		
[emim][NTf <sub>2</sub> ] F		81.1	35–40	23 ± 2	58 ± 2		
[C <sub>8</sub> H <sub>10</sub> BrN][NTf <sub>2</sub> ] G		85.7	30–35	27 ± 2	48 ± 3		
[C <sub>7</sub> H <sub>16</sub> NO <sub>2</sub> ][NTf <sub>2</sub> ] H		89.5	31–36	30 ± 2	58 ± 3		
[C <sub>25</sub> H <sub>54</sub> N][OTf] I		79.5	30–35	22 ± 2	53 ± 2		
[C <sub>6</sub> H <sub>16</sub> NO][NTf <sub>2</sub> ] J		89.1	30–35	28 ± 2	58 ± 2	–	
[C <sub>9</sub> H <sub>17</sub> NO <sub>2</sub> ][NTf <sub>2</sub> ] K	37.4	85.1	28–30	21 ± 2	63 ± 3	1.44	
[C <sub>10</sub> H <sub>20</sub> NO <sub>3</sub> ][NTf <sub>2</sub> ] L	39.4	86.6	33–40	22 ± 1	58 ± 3	1.44	
deionized water	72.5	110	85–90	40 ± 3	63 ± 3	1	0.89
NH <sub>4</sub> HCO <sub>3</sub> 25 mM	65.7	98	50–55	23 ± 2	65 ± 5	1	
+ 0.05% Tween20							
NH <sub>4</sub> HCO <sub>3</sub> 25 mM	38	81		20 ± 3	<i>i</i>	1	
+ 1% Tween20							

<sup>a</sup> All measurements were made at room temperature. <sup>b</sup> Surface tensions (mN·m) were measured with the pendant drop method on a drop shape analysis system G10/DSA10. <sup>c</sup> Nonactuated contact angles (°). <sup>d</sup> Contact angle at saturation (°) (all contact angles were measured using a commercial Digidrop GBX system, with droplets of 1  $\mu$ L). <sup>e</sup> Minimum actuation voltage ( $V_{\min}$ ) to displace a droplet of 0.4  $\mu$ L on a row of (800  $\mu$ m)<sup>2</sup> electrodes. <sup>f</sup> Saturation voltage ( $V_{\max}$ ). <sup>g</sup> Density in g·mL<sup>-1</sup>. <sup>h</sup> Kinematic viscosity (mm<sup>2</sup>/s) measured with Ubbelohde (Schott) micro-viscosimeter. <sup>i</sup> For buffer + 1% Tween 20, the electrowetting curve is impossible to record because of the evaporation and the very long equilibration time.

which is confirmed by our observation of the motions of these different liquids.

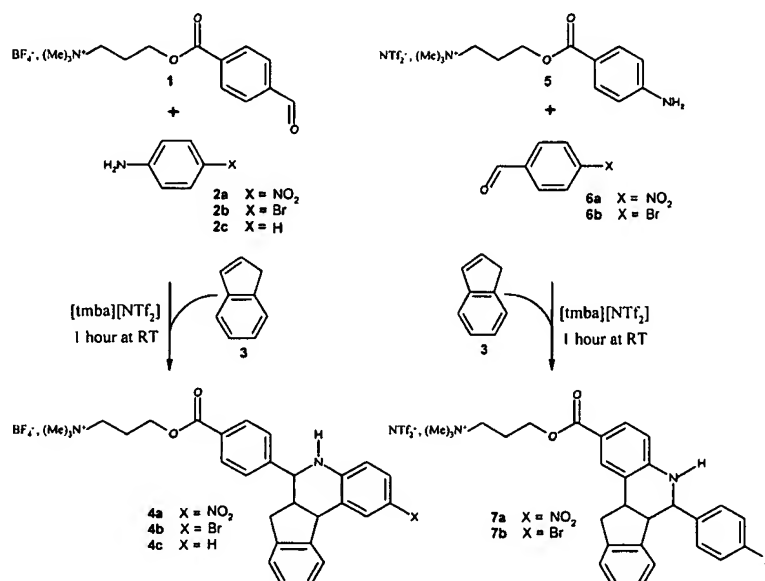
We first determined the two limits of the working potentials  $V_{\min}$  and  $V_{\max}$  (Table 1). The first limit is the minimum potential necessary to displace a droplet, and the second limit is the maximum potential above which the contact angle is stabilized (due to the saturation phenomenon (Figure 3)). Under air, ILs showed a wider working interval than water. Indeed, the minimum potential to move ionic liquid droplets (18–30 V) is lower than that of water (40 V), whereas the saturation threshold is similar for both. We assume that these smaller minimum potentials are due to a smaller surface tension,  $\gamma_{LG}$ , according to eq 1 and a

smaller hysteresis level of ionic liquids on Teflon. On the other hand,  $V_{\min}$  for ionic liquids and a biological buffer containing 1% of Tween 20 are similar.

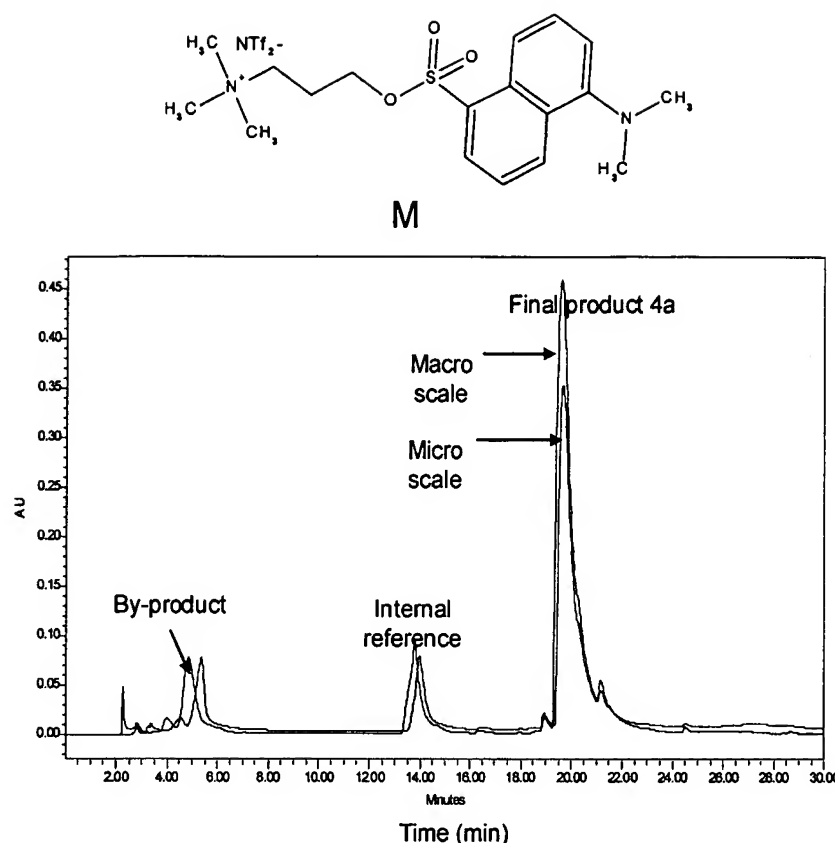
In addition, the elongation along the main axis of motion when the movement of the droplet starts is more important for ILs than for water. With our camera (25 pictures/s), we can see that the whole droplet of water is displaced when the next electrode is switched on, whereas for ionic liquids, the front of the droplet moves first and the back of the droplet follows. This is a consequence of the high viscosity of RTILs, their relatively high wettability (smaller contact angles), and their weak surface tension. Finally, these physical characteristics of ILs have two consequences: an important stretching of ionic liquids was possible, and the displacement speed of droplets is smaller in comparison with water. Motion speeds were measured by recording the droplet's motion on an open EWOD system under air, consisting of a row of (800  $\mu$ m)<sup>2</sup> electrodes. Typical values of RTIL motion speeds are between 1 and 10 mm/s, and we noted that the speed increases with the potential, whereas the maximum displacement speed of deionized water on the same chip has been evaluated at 120 mm/s.

**Application to a Multicomponent Reaction.** Since we showed that ionic liquids droplets can be moved by EWOD on a Teflon surface, the next step was to exploit this possibility to perform multicomponent chemical reactions. We chose a tetrahydroquinoline synthesis via a three-component reaction, as described by Grieco et al.<sup>36,37</sup> to validate this concept.<sup>38</sup>

This reaction was chosen for several reasons: (i) tetrahydroquinolines are an important class of biologically active compounds;<sup>39</sup> (ii) we wanted to demonstrate the feasibility of a relatively complex reaction; (iii) this reaction occurs rapidly at room temperature with a quantitative yield and has been demonstrated on solid supports.<sup>37</sup> In this reaction, an aniline reacts with an aldehyde in the presence of an electron-rich olefin and an acidic catalyst (trifluoroacetic acid (TFA)) to produce tetrahydroquinolines (Figure 4). To establish a reference, the reaction was first performed in a flask (macrovolume). The task-specific onium salt



**Figure 4.** Schematic representation of the reaction described by Grieco in a droplet microreactor.



**Figure 5.** Structure of internal reference, **M**, and comparison of the chromatograms of the macro- and microscale reactions after the reaction of **1** with **2a** and **3**. The observed byproduct in this chromatogram corresponds to a residual protonated *p*-nitroaniline, as confirmed by the mass spectrum in Figure 6.

**1** or **5** (0.2 M) was dissolved in a few milliliters of an ionic liquid matrix, such as ([tmba][NTf<sub>2</sub>]), then 2.5 equiv of benzaldehydic derivatives **2** or anilinic derivatives **6**, an excess of indene **3**, and an excess of trifluoroacetic acid were successively added to this solution. After incubation for 1 h, the condensation products **4** or **7** were characterized by NMR and ESI-MS. The times of retention of these products in HPLC were determined, as well.

These reactions were then transposed to the droplet microreactors. Hence, a 0.2-μL droplet of [tmba][NTf<sub>2</sub>] containing **1** or **5** and 10 equiv of TFA as described above was deposited on the chip and displaced by EWOD at 55 V. This droplet converged toward a second droplet of ionic liquid containing 2.5 equiv of the derivate **2** or **6**. After coalescence, the resulting droplet was merged with a third droplet containing an excess of indene. The reaction was incubated within 1 h at room temperature, then the final droplet was taken off the chip and washed with ether to eliminate the excess of **2** or **6** and **3**. The mixture was then injected into the HPLC, and the chromatogram was compared with that obtained in macrovolume. As shown in Figure 5, the retention time for the compound **4a** obtained in the droplet is similar to the retention time of the final product obtained in macrovolume. This result was confirmed by the ESI-MS analysis. Indeed, as shown in Figure 6, the obtained molecular ion for the compound **4a** at 486.5 amu is in agreement with the expected structure of the final product and identical to the product obtained in macrovolume. This result was confirmed by MS<sup>2</sup> and MS<sup>3</sup>

analyses of the molecular ion (see Supporting Information). The reaction with all the compounds described in Figure 4 gave correct results, too.

To quantify the reaction in droplets, we set up an HPLC method using an internal reference. Indeed, whereas the direct determination of the conversion rate is easy in macrovolume, this determination is blemished with errors when microvolumes are used. Thus, we introduced into the reactional mix a reference molecule **M**, inert versus the initial products, the final product, and the eventual byproducts, and this response in UV/HPLC is stable and reproducible. Then the ratio between the initial TSIL and the internal reference was determined at the start and at the end of the reaction. The conversion rate was estimated using the following equation,

$$T = 1 - X/X' \quad (4)$$

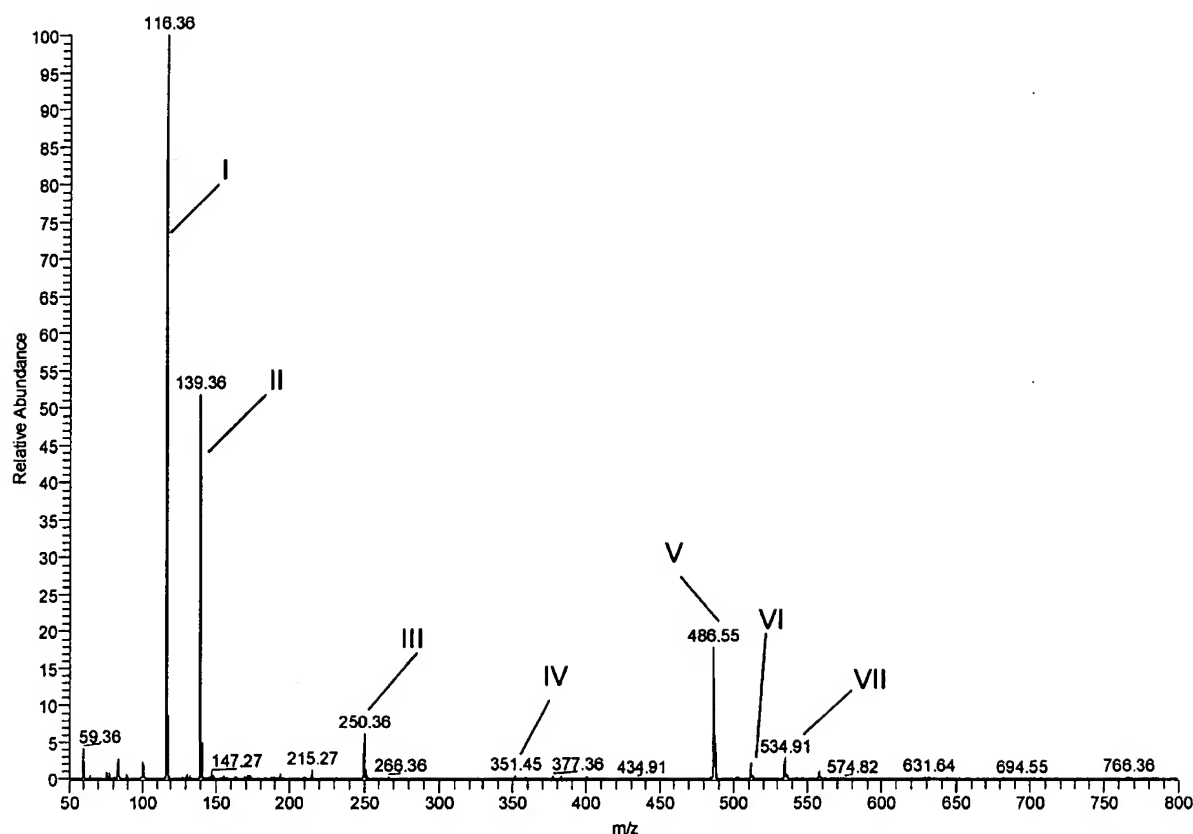
where *X* is the ratio between the HPLC traces of the initial TSIL and the internal reference of the starting solution and *X'* is the ratio between the HPLC traces of the final TSIL and the internal reference after 1 h of incubation.

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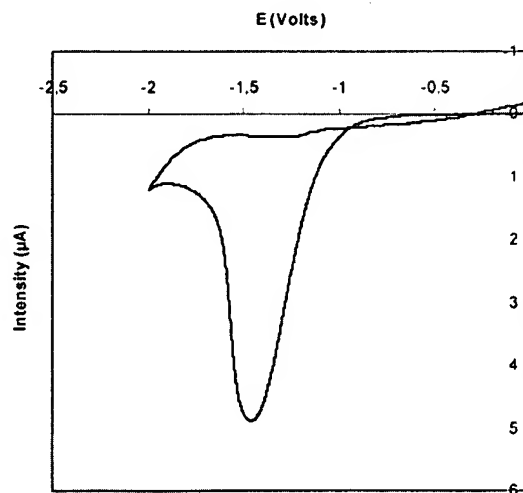


**Figure 6.** Mass spectrum of the droplet of ionic liquid after a 1-h incubation period at room temperature of **1**, **2a**, and **3** and then washing with ether. I,  $\text{tmba}^+$  ( $m/z$  theor = 116.14); II, protonated *p*-nitroaniline ( $m/z$  theor = 139.05); III, trace of the starting TSIL **1** ( $m/z$  theor = 250.14); IV, cation of the internal reference **M** ( $m/z$  theor = 351.17); V, molecular ion of **4a** ( $m/z$  theor = 486.24); VI, adduct  $[\text{2tmba}^+, \text{NTf}_2^-]^+$  ( $m/z$  theor = 512.20; found = 512.27); VII, adduct  $[\text{protonated } p\text{-nitroaniline}, \text{NTf}_2^-, \text{tmba}^+]^+$  ( $m/z$  theor = 535.11).

Then, with this method, we estimated a conversion rate between 98 and 100% according to the compounds. Moreover, good agreement between the reactions performed in the droplet and in the macrovolume was shown.

The on-line chip analysis was performed as the following. The droplet containing the final product **7a** was moved by EWOD toward an analytical area. The analysis was achieved by electrochemical detection between two gold catenaries on a chip (the chip is described in the Experimental Section). The first catenary permits the electro wetting and acts as a working electrode during the detection. The second one is both the counter electrode and the reference electrode. Thus, as shown in Figure 7, a cathodic peak, identical to that obtained in macrovolume, was observed at  $-1.46$  V versus the gold reference electrode. This signal corresponds to the reduction of the final product, and its magnitude reflects indirectly the concentration of the final product (Randles-Sevcik's relation).

Applying a similar approach as above, one can easily imagine a complex microsystem with an architecture inspired from Figure 2C.<sup>12</sup> This microsystem would enable the on-demand synthesis of organic compounds in very small quantities by parallel synthesis, combinatorial chemistry, or convergent synthesis. The TSIL droplet would be dispensed from a reservoir and react on the electrode row (reaction bus) with different reagents generated from secondary reservoirs. This could be performed in an open or closed system. Different reactions can be conducted in parallel on different reaction buses, and the final droplets can be mixed



**Figure 7.** Cyclic voltammogram of **7a** in  $[\text{tmba}][\text{NTf}_2]$  at a gold electrode ( $\phi = 25 \mu\text{m}$ );  $\nu = 50 \text{ mV s}^{-1}$ ; V versus gold electrode.

for convergent synthesis. This concept should bring important benefits, as compared to classical synthesis on microtiter plates, principally in terms of volumes of reagents and size of the equipment. Indeed, our approach should enable the researcher to achieve several reactions on a few square centimeters and avoid the use of bulky liquid-handling robots. Furthermore, future integration of analytical tools on the chip, such as real-time

monitoring of the reaction and final product analysis, should improve these systems, paving the way to fully integrated systems.

## CONCLUSIONS

In summary, we have described in this paper a powerful and flexible tool to synthesize minute amounts of organic compounds by using droplets of ionic liquids as microreactors and electrowetting as the fluidic motor. First, we checked that ionic liquids are compatible with EWOD actuation, even if their behavior is different from that of water. We were able to show that these droplets can be moved and combined on our system. This has been demonstrated with task-specific ionic liquids, TSILs, which when properly functionalized can be used as efficient soluble supports for supported organic synthesis. The multicomponent Grieco's reaction was used to validate the above hypothesis. It can be concluded that this original concept should impact many areas, notably combinatorial chemistry, parallel synthesis, opti-

mization of protocols, synthesis of dangerous products, and embedded chemistry on a portable device.

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## SUPPORTING INFORMATION AVAILABLE

Procedures for synthesis of ionic liquids and mass spectra after synthesis in droplets. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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## Task specific onium salts (TSOSs) as efficient soluble supports for Zard radical addition to olefins

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**Abstract**—Task specific onium salts (TSOSs), that is, functionalised ammonium salts, have been used as soluble supports to carry out intermolecular radical additions of xanthates to olefins and functional group interconversions. This methodology provides results by far superior to those reported with other soluble supports and allows for very easy purifications of reaction products. © 2007 Elsevier Ltd. All rights reserved.

Following pioneering Merrifield's work, solid-phase organic synthesis has developed enormously over the last 20 years.<sup>1</sup> Along with the heterogeneous nature of the polymeric supports arise a number of technical problems including slow and nonlinear reaction kinetics, reduced solvation, poor reaction sites accessibility, reactions monitoring and the low loading of these resins. Thus, soluble polymer supports such as polyethylene glycols, polyvinyl alcohol, soluble polystyrene<sup>2</sup> and dendritic polyglycerols<sup>3</sup> allow performing reactions in solution and have been demonstrated to be possible alternatives to solid supports. Although purification of the functionalised supports, usually by precipitation and filtration, is still an easy process, low loading capacity, aqueous solubility and retention of solvent traces remain problematic. Fluorous tagged molecules and solvents have also been successfully used but are costly and specialised technologies.<sup>4</sup> The arsenal of organic chemists still needs a valuable alternative to these soluble supports.

According to an exponentially growing literature, room temperature ionic liquids (RTILs) are a new category of solvents which have been shown to be a realistic substitute to volatile organic solvents for a large number of reactions.<sup>5</sup> Within this new area, recently reported task specific ionic liquids (TSILs) are particularly promising. Defined as ionic liquids bearing a functional group

covalently tethered either to the cation, the anion or both, they have been conferred special properties/reactivities and behave as reagents or catalysts.<sup>6</sup> In addition, we,<sup>7</sup> then others<sup>8</sup> thought to use functionalised onium salts (that is, task specific onium salts, TSOSs) as soluble supports for organic synthesis, whatever their melting point, provided that they are used as solutions either in molecular solvents or in ionic liquids. This basically led to the new concept of onium salts supported organic synthesis. This concept was successfully applied to a wide range of reactions such as cycloadditions,<sup>7</sup> multi-component reactions,<sup>7b</sup> palladium-catalyzed cross-coupling reactions<sup>7,8</sup> or peptide synthesis<sup>8,9</sup> to mention, but a few examples. Undoubtedly, applications will widen as they present convincing advantages over existing supports including (1) a very large number of possible combinations of functionalised cations and counter anions allowing a fine tuning of their properties (2) a facile reaction monitoring by using conventional analytical techniques such as routine NMR or HPLC, (3) easy separation of the supports from the target molecules after cleavage usually by simple extraction with a solvent or bulb-to-bulb distillation under vacuum (4) high loading capacity of both supports and solutions correlated to their low molecular weights and the use of highly concentrated solutions. Easy to prepare in large quantities at low cost, solutions of TSOSs can be pumped or cannulated therefore making automation possible.

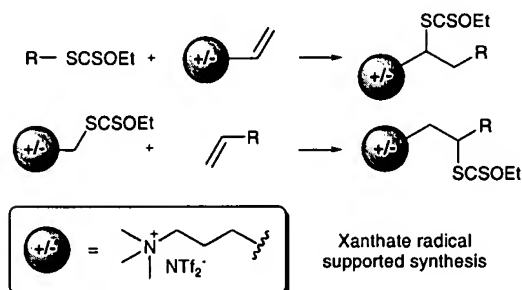
Radical reactions have become an important tool in organic synthesis<sup>10</sup> albeit used with limited success in supported synthesis. Because reaction kinetics differ strongly from those observed under homogenous

**Keywords:** Task specific ionic liquids; Zard radical addition; Onium salts supported organic synthesis; Xanthate.

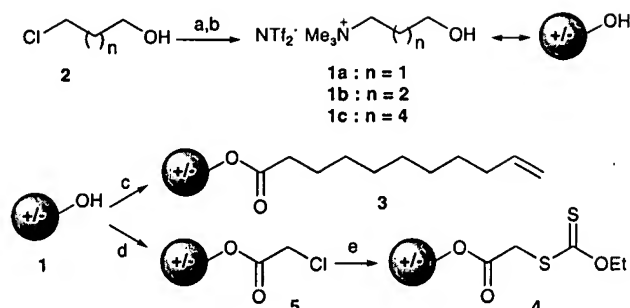
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conditions, radical reactions are particularly disfavoured on solid supports leading to addition of large amounts of radical initiator and longer reaction times.<sup>11</sup> Therefore, soluble supports have been employed to attempt circumventing these difficulties. The use of soluble supports is hampered by hydrogen abstraction  $\alpha$  to oxygens.<sup>12</sup> Zard and co-workers have studied intermolecular additions of radicals generated from xanthates to an olefin and functional group interconversions of supported xanthates as well (Scheme 1). Radical polymerizations have been well investigated in RTILs,<sup>14</sup> however, examples of radical reactions leading to non-polymeric molecules are scarce.<sup>15</sup> Therefore, the compatibility of RTILs with xanthate-based radical reactions was first investigated by carrying out radical addition of methoxycarbonylmethylxanthate to allyl phthalimide induced by dilauroyl peroxide (DLP) in some conventional ionic liquids. We were pleased to observe the formation of the adduct in four different ionic liquids based on ammonium and imidazolium cations under homogeneous conditions. In all solvents, the product was isolated in good yields ([tmba][NTf<sub>2</sub>], 71%) ([bmim][NTf<sub>2</sub>], 69%; [bmim][PF<sub>6</sub>], 68%; [bmim][BF<sub>4</sub>], 61%) as compared to an 83% yield reported for the same reaction in 1,2-dichloroethane.<sup>13</sup> DLP amount necessary for full conversion was higher (15–20 mol %) in the RTILs than for the same reaction in 1,2-DCE (5 mol % of DLP).<sup>13</sup> This could be explained by the higher viscosity of RTILs which would prevent the formed radicals from diffusing out of the solvent cage and subsequently facilitating their recombination.<sup>14,16</sup>

We next embarked on the TSOS's supported chemistry. Salts **1** were chosen as our starting platforms to support the reagents, either the xanthate or the olefin. The choice of the ammonium versus imidazolium salts was dictated by stability issues<sup>17</sup> and some practical advantages; namely, a simplified <sup>1</sup>H NMR spectrum beyond 3.7 ppm allowing easy routine NMR reaction monitoring. **1a–c** were classically obtained as clear free flowing oils by quarternisation of trimethylamine with terminal chloroalkanol-1-ol **2a–c**, followed by an anion metathesis with lithium triflimide in water (>95% yield for the two



Scheme 1. Radical reactions in onium salts supported organic synthesis.

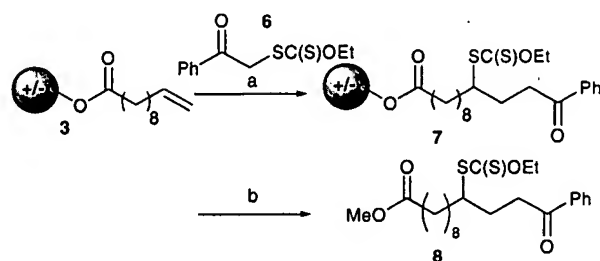


Scheme 2. Supports synthesis. Reagents and conditions: (a) NMe<sub>3</sub>, H<sub>2</sub>O/CH<sub>3</sub>CN, 70 °C, 14 h; (b) LiNTf<sub>2</sub>, H<sub>2</sub>O, rt, overnight; **1a**, 95%; **1b**, 94%; **1c**, 84% (c) **1c**, ClCO(CH<sub>2</sub>)<sub>8</sub>CH=CH<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>CN, 0 °C then rt, 2 h, 91%; (d) **1**, ClCOCH<sub>2</sub>Cl, K<sub>2</sub>CO<sub>3</sub>, 0 °C then 40 °C, 4 h, **5a**, 94%; **5b**, 99%; **5c**, 94%; (e) KSC(S)OEt, CH<sub>3</sub>CN, rt, 2 h, **4a**, 86%, **4b**, 96%, **4c**, 98%.

steps) (Scheme 2).<sup>5d</sup> Supported olefin **3** and xanthate **4a–c** were chosen for the sake of comparison with literature work<sup>13</sup> and synthesised by small modifications of described procedures facilitating TSOSs purification (Scheme 2).

Noticeably, loading capacities of supports **1a–c**, (respectively 2.51, 2.43 and 2.27 mmol/g) are higher than the usual PEG or soluble polystyrene ones. Additionally, unlike these supports, concentrated solutions of **1a–c**, useful for xanthate chemistry<sup>10</sup> can be used owing to **1**'s low molecular weight and good solubility in polar solvents. Intermolecular radical addition to the supported olefin **3c** was carried out in the presence of a 3-fold excess of xanthate **6** in 1,2-DCE at 80 °C in the presence of 13% molar of DLP as an initiator (Scheme 3).

Reaction monitoring by <sup>1</sup>H NMR showed complete conversion of **3c** after 4 h at 80 °C. Adduct **7c** was separated from excess starting xanthate **6** and non-supported impurities by washing several times with ether and then fully characterised (see Supplementary data) Cleavage from the support by transesterification in boiling acidic methanol led to the starting support **1c** and ester **8a–c** which could be easily separated by ether extraction and isolated pure in a 74% yield from **3c** after column chromatography.<sup>18</sup> This is close to the 80% yield reported for the reaction between xanthate **6** and 10-



Scheme 3. Radical addition to supported olefin. Reagents and conditions: (a) DLP (13 mol %), 1,2-DCE, 80 °C, 4 h; (b) HCl, MeOH, reflux, overnight, 74% from **3c**.



undecenoate reported by Zard and co-workers<sup>13</sup> Support **1c** could be recycled in a 92% yield and excellent purity. Interestingly, the same reaction with 10-undecenoic acid supported on a Wang resin and on Wang-like soluble polystyrene is reported to be sluggish with conversions below 80% even though higher xanthate/olefin ratios and more than 50 mol % of DLP have been used. Furthermore, a 9/1 mixture was obtained combining the linear adduct and a cyclic product arising from the cyclisation of the intermediate xanthate analogous to **7**.<sup>13</sup> Noteworthy, this tetralone formation was not observed using TSOS **3c** owing to a conserved discrepancy between xanthate transfer and cyclisation rates mimicking closely non-supported reaction media.

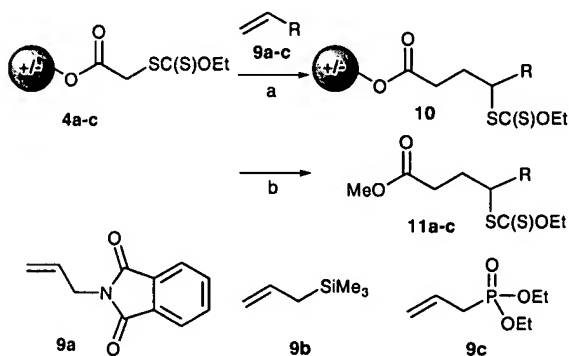
Reaction of **4a–c** with 1.3 equiv of olefin **9** in the presence of 10% of DLP was completed within 2 h leading to adducts **10aa–ac** in nearly quantitative yields (Table 1). These results are significantly better than using the same xanthate grafted on other soluble or insoluble supports<sup>13</sup> and comparable to non-supported version. Indeed, on a soluble polystyrene, 3 equiv of olefin and 40 mol % DLP are required to obtain complete conversion and only 54% of adduct **11a** were obtained after cleavage. With Wang resin as a support, it was necessary to use 10 equiv of **9a** and 32 mol % of DLP to get a 26% isolated yield of **10aa**.

Reaction scope has been investigated. Structurally diverse supports have been used for this reaction leading to similar conversions (Scheme 4), and among olefins allylphthalimide (**9a**), allyltrimethylsilane (**9b**) and allyldiethylphosphonate (**9c**) reacted equally well. Cleavage

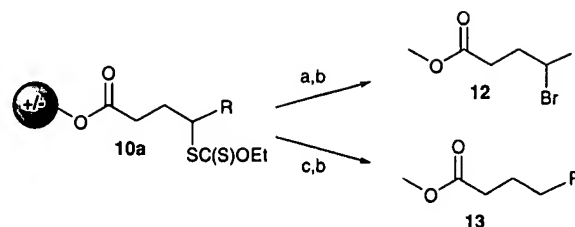
Table 1. Radical addition of the supported xanthate **4** to olefins **9**

Entry	<b>4</b>	Olefin	Addition (yield <sup>a</sup> %)	Cleavage (yield <sup>a</sup> %)
1	<b>4a</b>	<b>9a</b>	<b>10aa</b> (86)	<b>11a</b> (97)
2	<b>4b</b>	<b>9a</b>	<b>10ba</b> (86)	<b>11a</b> (47)
3	<b>4c</b>	<b>9a</b>	<b>10ca</b> (98)	<b>11a</b> (61)
4	<b>4a</b>	<b>9b</b>	<b>10ab</b> (90)	<b>11b</b> (80)
5	<b>4a</b>	<b>9c</b>	<b>10ac</b> (79)	<b>11c</b> (89)

<sup>a</sup> Isolated yield after purification.



Scheme 4. Radical addition of supported xanthate. Reagents and conditions: (a) DLP 10 mol %, **9a–c** 1.3 equiv 1,2-DCE, 80 °C; (b) DIPEA, MeOH, reflux, overnight.



Scheme 5. Further functionalisation of supported xanthates. Reagents and conditions: (a) C(BrMe<sub>2</sub>)COOEt (5 equiv), DLP (6 × 50 mol %), 1,2-DCE, 80 °C, 12 h; (b) HCl, MeOH, reflux, overnight; (c) DLP (13 × 10 mol %), isopropanol, 80 °C, 14 h.

from the support was completed after 16 h in refluxing anhydrous MeOH in the presence of DIPEA (0.5 equiv) leading to methyl esters **11a–c**, which were isolated in good yields (Scheme 4, Table 1). Noticeably, cleavage from longer chain supports is slightly less efficient (entries 2 and 3) but with the 3-carbon chain linker, good conversions were obtained, regardless of substituents. The radical addition of supported xanthates to olefins is a particularly stringent test for the three different supports discussed above. It appears that TSOSs supports are superior to the others<sup>13</sup> and might open the way to efficient supported radical chemistry allowing for very easy purification of products.

Xanthates are also useful for functional group interconversions via radical paths (Scheme 5).<sup>19</sup> Namely, **10a** could be converted into the corresponding bromide by heating with DLP and ethyl 2-bromoisobutyrate as a source of bromine.<sup>19d</sup> After cleavage with acidic methanol, product was isolated in a 41% yield over three steps from **4a** which is very good as compared to similar non-supported substrates.<sup>19d</sup> Reduction of the C–S bond in **10a** can also be done in isopropanol in the presence of a stoichiometric amount of DLP<sup>19a</sup> affording *N*-phthalimido methyl 4-aminobutanoate after cleavage in 56% isolated yield (two steps).

In addition to the use of ionic liquids as potential replacements for DCE in radical reactions, this study shows for the first time that task specific onium salts are efficient soluble supports to perform radical additions. Both the olefinic radical acceptor and the xanthate radical precursor can be supported by simple esterification of the ionic supports **1a–c**, easily prepared in two steps in high yields. Reactions are then carried out under homogeneous conditions in 1,2-DCE solutions, allowing easy <sup>1</sup>H NMR monitoring and separation of reactions products. This is also the first comparison reporting results obtained with TSOSs with those obtained from other supports such as Wang resins and soluble polystyrenes for a given reaction.

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### Supplementary data

Supplementary data includes experimental procedure for addition and physical data for all adducts. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.024.

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# Onium salt supported organic synthesis in water: application to Grieco's multicomponent reaction

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## Abstract

By using an ammonium chloride salt as water solubilizing moiety, our Onium Salts Supported Organic Synthesis strategy was extended to water as a solvent. This method allows for high loading capacities both of the supports and their solutions owing to low molecular weight of the onium salts and simplified purification steps as well.

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## 1. Introduction

Recently was developed a new strategy for supported organic synthesis, the Onium Salt Supported Organic Synthesis (OSSOS).<sup>1,2</sup> This strategy relies on the use of the physical properties of onium salts which confer a molecule, virtually with no vapor pressure.<sup>3</sup> Subsequently, this onium salt moiety could be used as a template for supported organic synthesis.<sup>4</sup> Indeed, this scaffold could be thought as the homogenous non polymeric analog of a classical resin used since 1963's Merrifield solid phase peptide supported synthesis.<sup>5</sup> Purifications were simplified to the extreme as easy filtration and washes usually afforded the product in pure form. If this feature was rather common for supported organic synthesis, several advantages were brought by the OSSOS. First, reaction conditions and yields were almost identical to those published under classical homogenous phase. This was probably attributable to both the tunable solubility of onium salts and their high loading capacities. As a matter of fact, the use of soluble support such as PolyEthyleneGlycols, i.e., PEGs, is allowing for performing reactions under homogeneous conditions, but owing to their high molecular weight (5000 typically), loading capacities are small (0.02 mmol g<sup>-1</sup>) and enforce performing reaction under high dilution conditions.<sup>6</sup> On the contrary, onium

salts' molecular weights are smaller (300–500 typically) and all experiments are carried out under standard 0.1–1 M concentration. Their structural simplicity is also allowing for using routine analysis techniques such as NMR, HPLC, and MS. Finally and more importantly, their nature is easily tunable depending which properties are essential for good reactivity. As an example, for reactions requiring strictly anhydrous conditions, a good choice would certainly be the use of an onium triflimide salt that can be dried easily and be lipophilic enough to dissolve organic reagents and mix with molecular organic solvent. This methodology has been successfully applied to a large number of reactions including peptide synthesis,<sup>7</sup> multicomponent reactions,<sup>8–10</sup> transition metal catalyzed reactions,<sup>4</sup> even radical addition.<sup>11</sup> The last example clearly demonstrated how the nature of the support could largely influences the outcome of the process.<sup>3,4</sup> Indeed, radical reactions are very sensitive to relative kinetics, and diffusion problem associated with the use of a resin often limited resin supported radical steps to polymerization reactions. However, when using a triflimide ammonium salt as a support, results are almost identical to those reported for classical conditions except that all the purification steps are eliminated.<sup>11</sup>

This point was critical when we tackled multicomponent reactions.<sup>12</sup> Often, non-supported versions are handicapped by side reactions leading to separation difficulties. Indeed, by supporting one reactant and therefore getting supported products, purification and removal of traces of impurities were largely improved. Nevertheless examples were scarce

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due to kinetic limitations in heterogeneous medium.<sup>13,14,10</sup> Grieco synthesis is a one pot multicomponent reaction between anilines, aldehydes, and electron rich alkenes providing tetrahydroquinolines in high yields under acid catalysis.<sup>15</sup> Mild catalytic conditions (often using lanthanide triflates)<sup>16</sup> could be used and were compatible with a wide range of aldehydes and anilines, therefore easily providing tetrahydroquinolines with large diversity. Armstrong and Carranco have already shown that Grieco's tetrahydroquinolines' synthesis was efficient on both Wang and Merrifield type resin. In the first case, after an  $\text{SnCl}_2$  catalyzed reaction, products were released from support using 15% TFA with good yields.<sup>17</sup> More recently, another application using scandium triflates with supported glyoxylic acid, anilines, and dihydropyridines provided tricycles in good yields.<sup>16</sup> We have already shown that this reaction could be supported on onium salts using triflimide counter anion.<sup>18,8</sup>

Here we would like to report the use of ammonium chloride salts as soluble support for Grieco's multicomponent reaction performed in pure water. Indeed, by adding a halide counter-anion to any of the three components supported on an onium salt, we were able to confer a good water solubility to the reactant thus allowing to perform the reaction in water. Adducts were then obtained under pure form via very simple purification steps. Water is now widely recognized as a good, cheap, and environmentally friendly solvent for organic synthesis.<sup>19–22</sup> It offers numerous advantages in terms of reactivity and selectivity and therefore has been used for almost all kind of reactions. Grieco's multicomponent reaction is one of them, and like several other multicomponent reactions, it has been shown that water has no detrimental effect on reactivity, and often increased yield and selectivity.<sup>23</sup> As an example, using heterogeneous phase supported acids (Montmorillonite or Bentonite),<sup>24</sup> water turned out to be the optimal solvent. Additionally, combining solid phase and organo aqueous medium allowed better yields and selectivities.<sup>16</sup>

## 2. Results

### 2.1. Support synthesis

In our case, we decided to support on-onium salts two of the three possible partners, namely the aniline and the benzaldehyde. Starting from trimethyl-3-hydroxypropylammonium chloride **1** both supported reagents were prepared in a couple of single pot high yielding steps. Supported aniline **2** was synthesized by coupling 4-nitrobenzoic acid with alcohol **1** followed by hydrogenation of the nitro function to the corresponding aniline. Onium salt supported benzaldehyde **3** was simply synthesized through an esterification of the corresponding benzoic acid with the same alcohol **1**. Alternatively, the ether linked benzaldehyde could be prepared following a two steps protocol involving a Williamson alkylation of 4-hydroxybenzaldehyde using 1-bromo-3-chloropropane followed by quaternization of trimethylamine with the obtained alkylchloride (Scheme 1).

Noteworthy, these supported reactants can be obtained in large scale in analytically pure form by simple washes with diethyl ether or acetone.

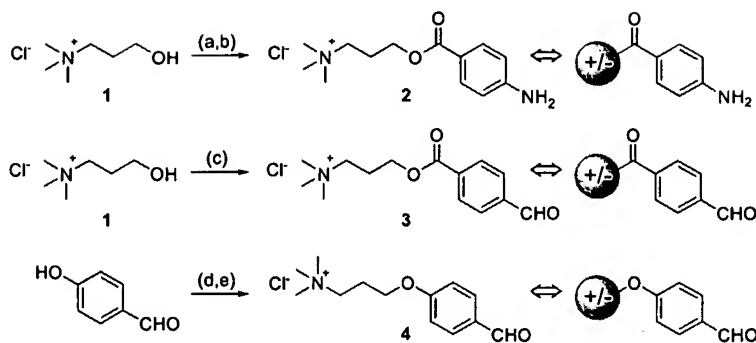
### 2.2. Tetrahydroquinolines' synthesis

We decided next to tackle the core of the project, namely Grieco's multicomponent reaction. To our delight, reactions proceeded extremely well under standard conditions in water. It demonstrated once again how flexible and reliable this OS-SOS strategy is. In the presence of a catalytic amount of TFA, products were isolated in good yield after several hours at room temperature (Scheme 2). Using ammonium chloride supported benzaldehyde **3** (Table 1, entries 1–6), reaction proceeded smoothly with cyclopentadiene (entries 1–4) and anilines. Namely, aniline (entry 1), 4-chloroaniline (entry 2), 4-nitroaniline (entry 3), 4-toluidine (entry 4) reacted equally well affording supported Grieco's adducts in 86%, 90%, 85%, and 90%, respectively. Reaction with indene was also efficient albeit slower, in these cases (entries 5 and 6) reaction with 4-chloro and 4-nitro anilines led to the expected tetrahydroquinolines in 84% and 80% yield, respectively. Concerning the use of supported aniline **2** (Table 1, entries 7–10), the same conditions were applied to the three components system and analogous adducts were obtained in good yields. Indeed reactions between **2**, cyclopentadiene, and parasubstituted benzaldehydes were efficiently producing expected heterocycles regardless of substitution (fluorine, entry 7, 78%; chlorine, entry 8, 92%; nitro, entry 9, 77%). Like mentioned previously, reaction with indene was slightly slower but afforded expected product in 85% yield (entry 10). Noteworthy, these products were obtained with only a simple purification procedure by side product extraction from the salt using diethyl ether.

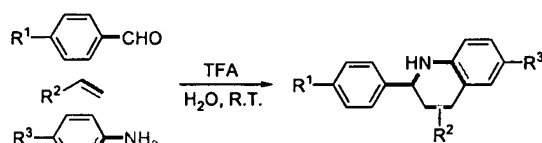
As an illustration of OSSOS simplicity for supported synthesis, standard  $^1\text{H}$  NMR experiments are sufficient for monitoring reactions. In addition to these promising results, we noticed that when reaction time was extended unnecessarily, a supported side product appeared in moderate quantity (up to 10%) resulting from the oxidation of expected products into quinolines. We decided to take advantage of this opportunity to develop an alternative procedure favoring this product.

### 2.3. Quinolines' synthesis

Indeed, we investigated for other catalyst and found that the use of tetrafluoroboric acid as catalyst afforded quinolines in good yields after several hours. If this reaction usually needs a second oxidation step using DDQ<sup>25</sup> or potassium permanganate,<sup>26</sup> in that case oxidation is probably linked to oxygen together with apparent hydrogen transfer from the transient imine resulting in the formation of the benzyl amine in a average 20% proportion. Due to its higher water solubility, this side product is easily eliminated by a simple washing. Both supported aldehydes reacted equally well. In a few hours, reaction between supported benzaldehydes **3** and **4**, indene, and various anilines afforded quinolines in good yields



Scheme 1. Preparation of ammonium chloride supported aniline and benzaldehyde. (a) 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CO<sub>2</sub>H, DCC, DMAP, CH<sub>3</sub>CN, rt; (b) Pd/C, H<sub>2</sub> (5 bar), H<sub>2</sub>O, rt, 92% (over two steps); (c) 4-CHOC<sub>6</sub>H<sub>4</sub>CO<sub>2</sub>H, DCC, DMAP, CH<sub>3</sub>CN, rt (96%); (d) Br(CH<sub>2</sub>)<sub>3</sub>Cl, K<sub>2</sub>CO<sub>3</sub>, acetone, Δ, 87%; (e) NMe<sub>3</sub> (50% aqueous), CH<sub>3</sub>CN, 70 °C, 18 h, 98%.



Scheme 2. Grieco's tetrahydroquinolines synthesis.

(Table 2). Halide substituted anilines (entries 4, 5, 7, and 8) yielded the expected products and no differences in reactivities were observed between electron donating and withdrawing substituted aromatic amines (entries 3 and 6). Same behavior was observed between ether (entry 2) and ester (entry 9) linkage although ester appeared slightly sensitive to hydrolysis.

### 3. Conclusion

Indeed, the Onium Salt Supported Organic Synthesis methodology turned out to be perfectly suitable for multicomponent reactions, a key feature for parallel synthesis. When an ester linkage is used heterocycles release from the support is performed under previously described conditions<sup>8,1,2</sup> (NH<sub>3</sub>, MeOH). Additionally, both reagents (aniline and aldehyde) can be grafted and reactions are performed hereafter with equal efficiency and ease. Moreover, taking advantages of the flexibility of the onium salt part of the molecule, we managed to confer the assembly a good water-solubility enabling the possibility to perform many type of reactions in pure water. This has been highlighted in this manuscript by Grieco's multicomponent condensation and a new quinolines' one-step synthesis. This broadens the use of water as a reaction solvent which is often restricted by poor substrate solubility.

### 4. Experimental

#### 4.1. General methods

All reactions were carried out using standard Schlenk techniques under argon. All other standard chemicals were purchased from ACROS chemicals or Aldrich Chemical Co. and used without further purification. Reactions were monitored by gas chromatography (GC–MS) (GC system: HP 6890 series, Mass selective detector HP 5973) using a capillary

column DB-5MS. Melting points were determined on an electrothermal IA9300 digital melting point instrument. NMR spectra were recorded on a Bruker ARX 200 (<sup>1</sup>H: 200.13 MHz, <sup>13</sup>C: 50.32 MHz) or AC 300 (<sup>1</sup>H: 300.13 MHz), <sup>1</sup>H chemical shifts (δ) are given in parts per million relative to TMS as internal standard, *J* values in hertz, <sup>13</sup>C chemical shifts are given relative to the central signal of CDCl<sub>3</sub> at 77.0 ppm. High resolution mass spectra measurements were performed at the Centre Regional de Mesures Physiques de l'Ouest (C.R.M.P.O, University of Rennes 1) using a Micro-mass ZABSpec TOF with EBE OA TOF geometry with LSIMS Ionization (Liquid Secondary Ion Mass Spectrometry) at 8 kV with Cs<sup>+</sup> gun in *m*-nitrobenzyl alcohol (*m*NBA).

#### 4.1.1. General procedure for Grieco condensation with supported aniline 2 (procedure A)

To a solution of amine (100 mg, 0.36 mmol) 2 in 0.2 mL of H<sub>2</sub>O were successively added the benzaldehyde (1.1 equiv), the olefin (10 equiv), and TFA (1.2 equiv). After 2 h at room temperature, volatiles were removed under reduced pressure. Upon addition of Et<sub>2</sub>O, residue crystallized. Crystals were filtered off and washed with 3×2 mL of Et<sub>2</sub>O to afford product 6 in pure form.

#### 4.1.2. General procedure for Grieco condensation with supported benzaldehyde 3 (procedure B)

To a solution of aldehyde (100 mg, 0.35 mmol) 3 in 0.2 mL of H<sub>2</sub>O were successively added aniline (1.1 equiv), olefin (10 equiv), and TFA (1.2 equiv). After 2 h at room temperature, solvent was removed under reduced pressure. Upon addition of Et<sub>2</sub>O, residue crystallized. Crystals were filtered off and washed with 3×2 mL of Et<sub>2</sub>O to afford product 5 in pure form.

#### 4.1.3. General procedure for quinolines' synthesis (procedure C)

To a solution of supported aldehyde 4 (or respectively 3) (100 mg, 0.38 mmol) in 0.2 mL of H<sub>2</sub>O were successively added aniline (1.1 equiv), olefin (10 equiv), and HBF<sub>4</sub> (1.2 equiv). After 24 h at room temperature, solvent and volatiles were removed under reduced pressure. Upon addition of Et<sub>2</sub>O, residue crystallized. After filtration, recrystallization in acetone afforded product 7 (respectively 8) in pure form.

Table 1  
 Grieco's three components reaction using supported benzaldehyde 3 and aniline 2

Entry	Aldehyde	Aniline	Olefin	Product	Yield %
1					86
2					90
3					85
4					90
5					84
6					80
7					78
8					92
9					77
10					85

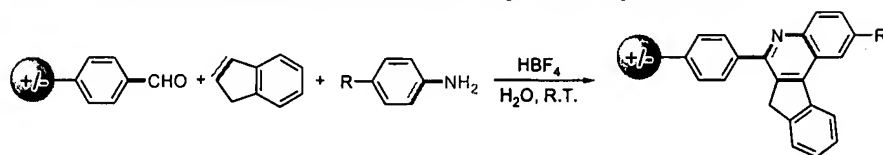
## 4.2. Support synthesis

### 4.2.1. [3-(4-Aminobenzoyloxy)propyl]trimethylammonium chloride 2

To a mixture of alcohol 1 (5.00 g, 32.57 mmol) in 100 mL of dry acetonitrile were added DCC (48.5 mmol, 1.5 equiv), 4-nitrobenzoic acid (48.5 mmol, 1.5 equiv), and DMAP

(6.52 mmol, 0.2 equiv). After 4 h at room temperature, solvents were removed under vacuum and product was extracted with 3×30 mL of Et<sub>2</sub>O to afford an oil used without further purification in the next step. <sup>1</sup>H NMR (200 MHz, D<sub>2</sub>O): 2.18–2.43 (m, 2H), 3.15 (s, 9H), 3.38–3.60 (m, 2H), 4.43 (t, 2H, *J*=5.8 Hz), 8.02 (dd, 2H, *J*<sub>1</sub>=1.9 Hz, *J*<sub>2</sub>=7.1 Hz), 8.18 (dd, 2H, *J*<sub>1</sub>=2.1 Hz, *J*<sub>2</sub>=6.9 Hz), <sup>13</sup>C NMR (50 MHz,

Table 2

Quinolines synthesis from supported benzaldehydes **3** and **4**, indene, and anilines using a three component reaction

Entry	Aldehyde	Aniline	Olefin	Product	Yield %
1					60
2					62
3					60
4					57
5					56
6					50
7					62
8					60
9					59



D<sub>2</sub>O): 22.6, 53.5 (t,  $J_{C-N}=4.0$  Hz), 63.4, 64.1, 123.8, 130.9, 134.94, 150.3, 166.0. To a solution of [3-(4-nitrobenzoyloxy)propyl]trimethylammonium chloride (8.5 g, y mmol) in 100 mL of water was added x mg of 5% Pd/C (1% molar). The mixture was stirred under a hydrogen atmosphere (5 bar) for 48 h. After filtration and concentration under reduced pressure, 6.95 g of a white solid were obtained (90% yield, two steps). Mp 120–122 °C. <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O): 2.10–2.25 (m, 2H), 3.09 (s, 9H), 3.32–3.45 (m, 2H), 4.48 (t, 2H,  $J=6.1$  Hz), 6.75 (d, 2H,  $J=7.8$  Hz), 7.72 (d, 2H,  $J=7.8$  Hz), <sup>13</sup>C NMR (75 MHz, D<sub>2</sub>O): 22.6, 53.47 (t,  $J_{C-N}=4.1$  Hz), 61.9, 64.2, 114.9, 118.2, 132.0, 153.0, 168.8. HRMS (FAB) C<sub>13</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub>: calculated 237.1603, found: 237.1603.

#### 4.2.2. [3-(4-Formylbenzoyloxy)propyl]trimethylammonium chloride 3

To a solution of 1 (2 g, 13 mmol) in 100 mL of CH<sub>3</sub>CN were added DCC (19.5 mmol, 1.5 equiv), 4-formylbenzoic acid (19.5 mmol, 1.5 equiv), and DMAP (2.6 mmol, 0.2 equiv). After 2 h at room temperature, solvent was removed and the residue was extracted with 3×30 mL of H<sub>2</sub>O. Aqueous phase was washed with 3×30 mL of Et<sub>2</sub>O and concentrated under reduced pressure to afford a yellow solid (yield 96%). Mp 120–122 °C. <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O): 2.18–2.31 (m, 2H), 3.09 (s, 9H), 3.42–3.48 (m, 2H), 4.37 (t, 2H,  $J=5.8$  Hz), 7.91 (d, 2H,  $J=8.2$  Hz), 8.06 (d, 2H,  $J=8.2$  Hz), 9.91 (s, 1H), <sup>13</sup>C NMR (75 MHz, D<sub>2</sub>O): 22.1, 53.0 (t,  $J_{C-N}=4$  Hz), 62.6, 63.7, 129.6, 129.91, 134.0, 138.6, 166.6, 195.1. HRMS (FAB) C<sub>14</sub>H<sub>20</sub>NO<sub>3</sub>Cl: calculated 250.1443, found: 250.1451 (C<sup>+</sup>).

#### 4.2.3. 3-{[4-(Formylphenoxy)propyl]trimethylammonium chloride 4

To a solution of 4-hydroxybenzaldehyde (10.0 g, 82 mmol) in 125 mL of acetone were added 1-bromo-4-chloro-propane (164 mmol, 2 equiv, 16.2 mL) and K<sub>2</sub>CO<sub>3</sub> (11.3 g, 82 mmol, 1 equiv). After 18 h under refluxing conditions, solvent was removed and the residue purified by distillation on a Kugelrohr apparatus ( $T=60$  °C,  $P=0.1$  mmHg) yielding 16.2 g of a colorless oil (yield 87%) corresponding to 4-(3-chloropropoxy)benzaldehyde. <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>): 2.25–2.40 (m, 2H), 3.81 (t, 2H,  $J=6.2$  Hz), 4.25 (t, 2H,  $J=6.2$  Hz), 7.03 (d, 2H,  $J=8.7$  Hz), 7.88 (d, 2H,  $J=8.7$  Hz), 9.90 (s, 1H), <sup>13</sup>C NMR (75 MHz, acetone-*d*<sub>6</sub>): 32.0, 41.3, 64.8, 114.8, 130.4, 131.6, 163.7, 190.3. To a solution of 10.0 g (50.4 mmol) of this oil in acetonitrile (20 mL) was added in a schlenk tube 13.8 mL of an aqueous solution of trimethylamine (50%). After 18 h at 70 °C, the reacting mixture was concentrated under reduced pressure. The obtained residue was washed with acetone (3×10 mL) then dried under high vacuum to afford the expected product in 98% as a yellow solid. Mp 82–84 °C. <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O): 2.21–2.32 (m, 2H), 3.11 (s, 9H), 3.42–3.58 (m, 2H), 4.19 (t, 2H,  $J=5.4$  Hz), 7.03 (d, 2H,  $J=8.6$  Hz), 7.85 (d, 2H,  $J=8.6$  Hz), 9.71 (s, 1H), <sup>13</sup>C NMR (75 MHz, D<sub>2</sub>O): 22.5, 52.9 (t,  $J=4.0$  Hz), 63.8, 64.9, 115.0,

129.3, 132.7, 163.7, 194.8. HRMS (FAB) C<sub>13</sub>H<sub>20</sub>NO<sub>2</sub>Cl: calculated 222.1494, found: 222.1494 (C<sup>+</sup>).

#### 4.3. Tetrahydroquinolines

##### 4.3.1. {3-[4-(3a,4,5,9b-Tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoyloxy]propyl}trimethylammonium chloride 5a

Following procedure A using aniline and cyclopentadiene, a light brown solid was obtained in 86% yield. Mp 128–130 °C. <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>): 1.61–1.74 (m, 1H), 2.26–2.43 (m, 2H), 2.48–2.63 (m, 1H), 2.98–3.11 (m, 1H), 3.21 (s, 9H), 3.54–3.61 (m, 2H), 4.10–4.13 (m, 1H), 4.46 (t, 2H,  $J=5.9$  Hz), 4.68–4.69 (m, 1H), 5.56–5.63 (m, 1H), 5.83–5.92 (m, 1H), 6.67–6.75 (m, 2H), 6.91–6.96 (m, 1H), 7.03 (d, 1H,  $J=7.6$  Hz), 7.63 (d, 2H,  $J=8.3$  Hz), 8.08 (d, 2H,  $J=8.3$  Hz), <sup>13</sup>C NMR (75 MHz, acetonitrile-*d*<sub>3</sub>): 23.5, 31.1, 46.1, 46.6, 52.4 (t,  $J_{C-N}=4.0$  Hz), 57.5, 61.3, 63.7, 116.0, 118.8, 122.0, 125.8, 126.5, 128.5, 129.1, 129.4, 129.8, 134.2, 145.4, 148.9, 166.3. HRMS (FAB) [C<sub>25</sub>H<sub>31</sub>N<sub>2</sub>O<sub>2</sub>][Cl]: calculated 391.2385, found: 391.2388 (C<sup>+</sup>).

##### 4.3.2. {3-[4-(8-Chloro)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoyloxy]propyl}trimethylammonium chloride 5b

Following procedure A using 4-chloroaniline and cyclopentadiene, a light brown solid was obtained in 90% yield. Mp 148–150 °C. <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>): 1.58–1.70 (m, 1H), 2.22–2.42 (m, 2H), 2.45–3.61 (m, 1H), 2.93–3.09 (m, 1H), 3.21 (s, 9H), 3.56–3.61 (m, 2H), 4.03–4.16 (m, 1H), 4.46 (t, 2H,  $J=5.9$  Hz), 4.66–4.47 (m, 1H), 5.69–5.72 (m, 1H), 5.81–6.93 (m, 1H), 6.71 (d, 1H,  $J=8.5$  Hz), 6.89 (dd, 1H,  $J_1=2.1$  Hz,  $J_2=8.5$  Hz), 7.02 (s, 1H), 7.61 (d, 2H,  $J=8.2$  Hz), 8.05 (d, 2H,  $J=8.2$  Hz), <sup>13</sup>C NMR (75 MHz, methanol-*d*<sub>4</sub>): 23.8, 32.5, 47.0, 47.6, 53.6 (t,  $J_{C-N}=4$  Hz), 58.9, 62.7, 65.1, 117.3, 120.1, 127.2, 127.9, 129.3, 129.6, 130.1, 130.4, 130.8, 135.6, 146.9, 150.3, 166.3. HRMS (FAB) [C<sub>25</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>Cl][Cl]: calculated 425.1995, found: 425.2000 (C<sup>+</sup>).

##### 4.3.3. {3-[4-(8-Nitro)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoyloxy]propyl}trimethylammonium chloride 5c

Following procedure A using 4-nitroaniline and cyclopentadiene, a light brown solid was obtained in 85% yield. Mp 144–146 °C. <sup>1</sup>H NMR (300 MHz, methanol-*d*<sub>4</sub>): 1.63–1.79 (m, 1H), 2.23–2.37 (m, 2H), 2.39–2.56 (m, 1H), 3.11–3.25 (m, 1H), 3.47 (s, 9H), 3.90–3.96 (m, 2H), 4.09–4.16 (m, 1H), 4.49 (t, 2H,  $J=5.8$  Hz), 4.78–4.84 (m, 1H), 5.63–5.73 (m, 1H), 5.88–5.98 (m, 1H), 6.76 (d, 1H,  $J=8.6$  Hz), 7.66–7.78 (m, 4H), 8.26 (d, 2H,  $J=8.6$  Hz), <sup>13</sup>C NMR (75 MHz, methanol-*d*<sub>4</sub>): 24.0, 32.5, 46.7, 47.7, 53.7 (t,  $J_{C-N}=4$  Hz), 57.7, 62.2, 65.3, 116.5, 120.1, 124.5, 125.9, 128.7, 129.5, 130.9, 132.2, 135.3, 148.3, 151.3, 152.1, 168.2. HRMS (FAB) [C<sub>25</sub>H<sub>30</sub>N<sub>3</sub>O<sub>4</sub>][Cl]: calculated 436.2236, found: 436.2239 (C<sup>+</sup>).



4.3.4. {3-[4-(8-Methyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta-  
[c]quinolin-4-yl]benzoyloxy}propyl}trimethylammonium  
chloride 5d

Following procedure A using 4-methylaniline and cyclopentadiene, a light brown solid was obtained in 90% yield. Mp 130–132 °C. <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>): 1.70–1.85 (m, 1H), 2.26 (s, 3H), 2.28–2.36 (m, 2H), 2.46–2.63 (m, 1H), 3.04–3.13 (m, 1H), 3.21 (s, 9H), 3.52–3.66 (m, 2H), 4.07–4.19 (m, 1H), 4.46 (t, 2H, *J*=5.9 Hz), 4.71–4.82 (m, 1H), 5.57–5.68 (m, 1H), 5.83–5.93 (m, 1H), 6.87 (d, 1H, *J*=8.3 Hz), 6.98 (s, 1H), 7.32 (d, 1H, *J*=8.3 Hz), 7.60 (d, 2H, *J*=8.3 Hz), 8.09 (d, 2H, *J*=8.3 Hz), <sup>13</sup>C NMR (75 MHz, acetone-*d*<sub>6</sub>): 20.8, 23.9, 32.5, 45.2, 47.6, 53.6 (t, *J*<sub>C–N</sub>=4 Hz), 60.0, 62.8, 65.1, 119.5, 123.8, 127.8, 128.3, 130.2, 130.6, 130.8, 130.9, 131.7, 135.1, 140.6, 147.8, 167.4. HRMS (FAB) [C<sub>26</sub>H<sub>33</sub>N<sub>2</sub>O<sub>2</sub>][Cl]: calculated 405.2542, found: 405.2536 (C<sup>+</sup>).

4.3.5. {3-[4-(2-Chloro)-6,6a,7,11b-tetrahydro-6H-indeno-  
[2,1-*c*]quinolin-6-yl]benzoyloxy}propyl}trimethyl-  
ammonium chloride 5e

Following procedure A using 4-chloroaniline and indene, a yellow solid was obtained in 84% yield. Mp 198–200 °C. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): 2.15–2.36 (m, 3H), 2.98–3.05 (m, 1H), 3.13 (s, 9H), 3.45–4.61 (m, 2H), 4.35 (t, 2H, *J*=5.6 Hz), 4.52 (d, 1H, *J*=7.5 Hz), 4.73 (s, 1H), 6.74 (d, 1H, *J*=8.6 Hz), 6.94 (dd, 1H, *J*<sub>1</sub>=2.2 Hz, *J*<sub>2</sub>=8.5 Hz), 7.01–7.21 (m, 3H), 7.26 (s, 1H), 7.61–7.71 (m, 3H), 8.05 (d, 2H, *J*=8.3 Hz), <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): 22.1, 37.1, 45.0, 46.7, 52.5 (t, *J*<sub>C–N</sub>=4.0 Hz), 55.6, 61.7, 62.7, 114.9, 121.6, 123.8, 125.2, 125.4, 126.5, 127.2, 127.4, 127.6, 129.0, 129.9, 137.3, 142.0, 145.9, 147.3, 152.6, 165.9. HRMS (APCI) [C<sub>29</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>Cl][Cl]: calculated 475.2152, found: 475.2159 (C<sup>+</sup>).

4.3.6. {3-[4-(2-Nitro)-6,6a,7,11b-tetrahydro-6H-indeno-  
[2,1-*c*]quinolin-6-yl]benzoyloxy}propyl}trimethyl-  
ammonium chloride 5f

Following procedure A using 4-nitroaniline and indene, a yellow solid was obtained in 80% yield. Mp 184–186 °C. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): 2.07–2.28 (m, 3H), 2.78–2.94 (m, 1H), 3.10 (s, 9H), 3.44–3.56 (m, 2H), 4.37 (t, 2H, *J*=5.6 Hz), 4.58 (d, 1H, *J*=7.5 Hz), 4.84 (s, 1H), 6.82 (d, 1H, *J*=8.9 Hz), 7.02–7.14 (m, 2H), 7.22 (t, 1H, *J*=7.2 Hz), 7.61–7.74 (m, 4H), 7.84 (dd, 1H, *J*<sub>1</sub>=2.3 Hz, *J*<sub>2</sub>=8.9 Hz), 8.06 (d, 2H, *J*=8.5 Hz), <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): 22.1, 30.8, 44.2, 46.0, 52.2 (t, *J*<sub>C–N</sub>=4.0 Hz), 54.9, 61.8, 62.7, 114.4, 121.1, 123.3, 124.7, 124.9, 126.0, 126.3, 126.9, 127.1, 128.5, 129.4, 136.8, 141.5, 145.4, 146.8, 152.1, 165.9. HRMS (APCI) [C<sub>29</sub>H<sub>32</sub>N<sub>3</sub>O<sub>4</sub>][Cl]: calculated 486.2392, found: 486.2384 (C<sup>+</sup>).

4.3.7. {3-[4-(4-Fluorophenyl)-3a,4,5,9b-tetrahydro-  
3H-cyclopenta[c]quinoline-8-carbonyloxy]propyl}-  
trimethylammonium chloride 6a

Following procedure B using 4-fluorobenzaldehyde and cyclopentadiene, a light brown solid was obtained in 78% yield. Mp 112–114 °C. <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>): 1.65–1.80 (m, 1H), 2.33–2.54 (m, 3H), 2.92–3.11 (m, 1H), 3.45 (s, 9H),

3.76–3.87 (m, 2H), 4.07–4.13 (m, 1H), 4.39 (t, 2H, *J*=5.9 Hz), 4.77 (s, 1H), 5.59–5.68 (m, 1H), 5.90–6.01 (m, 1H), 6.86 (d, 1H, *J*=8.5 Hz), 7.09–7.23 (d, 2H, *J*=8.6 Hz), 7.46–7.55 (m, 2H), 7.62 (dd, 1H, *J*<sub>1</sub>=1.8 Hz, *J*<sub>2</sub>=8.5 Hz), 7.72 (s, 1H), <sup>13</sup>C NMR (75 MHz, methanol-*d*<sub>4</sub>): 23.3, 32.5, 46.7, 47.3, 53.6 (t, *J*<sub>C–N</sub>=4.0 Hz), 57.5, 62.1, 65.2, 115.9, 116.1, 119.6, 125.9, 129.3, 129.4, 131.0, 132.2, 135.3, 139.5, 152.6, 163.3 (t, *J*<sub>C–F</sub>=244 Hz), 168.3. HRMS (FAB) [C<sub>25</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>F][Cl]: calculated 409.2291, found: 409.2296 (C<sup>+</sup>).

4.3.8. {3-[4-(4-Chlorophenyl)-3a,4,5,9b-tetrahydro-  
3H-cyclopenta[c]quinoline-8-carbonyloxy]propyl}-  
trimethylammonium chloride 6b

Following procedure B using 4-chlorobenzaldehyde and cyclopentadiene, a pale greenish solid was obtained in 80% yield. Mp 166–168 °C. <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>): 1.60–1.78 (m, 1H), 2.32–2.54 (m, 3H), 2.93–3.14 (m, 1H), 3.45 (s, 9H), 3.74–3.96 (m, 2H), 4.07–4.20 (m, 1H), 4.39 (t, 2H, *J*=5.8 Hz), 4.78 (s, 1H), 5.54–5.67 (m, 1H), 5.72–5.80 (m, 1H), 5.87–6.03 (m, 1H), 6.87 (d, 1H, *J*=8.3 Hz), 7.42 (d, 2H, *J*=8.5 Hz), 7.51 (d, 2H, *J*=8.5 Hz), 7.63 (dd, 1H, *J*<sub>1</sub>=1.4 Hz, *J*<sub>2</sub>=8.3 Hz), 7.73 (s, 1H), <sup>13</sup>C NMR (75 MHz, methanol-*d*<sub>4</sub>): 22.6, 31.1, 45.3, 45.7, 52.3 (t, *J*<sub>C–N</sub>=4 Hz), 56.1, 60.7, 63.8, 114.8, 118.3, 124.5, 127.8, 128.0, 128.1, 129.6, 130.8, 132.4, 133.9, 140.9, 151.1, 166.8. HRMS (FAB) [C<sub>25</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>Cl][Cl]: calculated 425.1995, found: 425.2000 (C<sup>+</sup>).

4.3.9. {3-[4-(4-Nitrophenyl)-3a,4,5,9b-tetrahydro-  
3H-cyclopenta[c]quinoline-8-carbonyloxy]propyl}-  
trimethylammonium chloride 6c

Following procedure B using 4-nitrobenzaldehyde and cyclopentadiene, a light brown solid was obtained in 77% yield. Mp 120–122 °C. <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>): 1.61–1.82 (m, 1H), 2.39–2.63 (m, 3H), 3.11–3.29 (m, 1H), 3.47 (s, 9H), 3.86–4.07 (m, 2H), 4.49 (t, 2H, *J*=5.8 Hz), 4.69–4.76 (m, 1H), 4.81 (s, 1H), 5.53–5.60 (m, 1H), 5.63–5.72 (m, 1H), 5.83–5.98 (m, 1H), 7.16–7.21 (m, 2H), 7.66 (dd, 2H, *J*<sub>1</sub>=2.2 Hz, *J*<sub>2</sub>=8.5 Hz), 8.09 (dd, 2H, *J*<sub>1</sub>=2.2 Hz, *J*<sub>2</sub>=8.5 Hz), <sup>13</sup>C NMR (75 MHz, methanol-*d*<sub>4</sub>): 21.4, 30.0, 42.3, 44.7, 51.2 (t, *J*<sub>C–N</sub>=4.0 Hz), 55.4, 60.3, 62.8, 112.8, 118.8, 119.0, 125.3, 125.4, 127.5, 128.4, 129.9, 130.4, 130.5, 147.0, 147.1, 165.2. HRMS (FAB) [C<sub>25</sub>H<sub>30</sub>N<sub>3</sub>O<sub>4</sub>][Cl]: calculated 436.2236, found: 436.2239 (C<sup>+</sup>).

4.3.10. {3-[6-(4-Nitrophenyl)-5,6a,7,11b-tetrahydro-6H-  
indeno[2,1-*c*]quinoline-2-carbonyloxy]propyl}-  
trimethylammonium chloride 6d

Following procedure B using 4-nitrobenzaldehyde and indene, a yellow solid was obtained in 85% yield. Mp 180–182 °C. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): 2.23–2.38 (m, 1H), 2.40–2.54 (m, 2H), 3.05–3.38 (m, 2H), 3.45 (s, 9H), 3.78–3.90 (m, 2H), 4.30–4.54 (m, 2H), 4.60 (d, 1H, *J*=7.5 Hz), 5.04–5.12 (m, 1H), 6.15–6.20 (m, 1H), 6.83 (d, 1H, *J*=8.3 Hz), 7.02–7.13 (m, 3H), 7.60–7.70 (m, 2H), 7.85 (d, 2H, *J*=9.1 Hz), 7.95–8.01 (m, 1H), 8.30 (d, 2H, *J*=9.1 Hz), <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): 22.6, 31.3, 44.7, 46.5, 52.7 (t, *J*<sub>C–N</sub>=4 Hz), 55.4, 62.3, 63.2, 114.9, 121.6,

123.8, 125.2, 125.5, 126.5, 127.1, 127.4, 127.6, 129.0, 129.9, 137.3, 142.0, 145.9, 147.3, 152.6, 165.9. HRMS (FAB) [C<sub>29</sub>H<sub>32</sub>N<sub>3</sub>O<sub>4</sub>][Cl]: calculated 486.2392, found: 486.2384 (C<sup>+</sup>).

#### 4.4. Quinolines

##### 4.4.1. {3-[4-(7H-Indeno[2,1-c]quinolin-6-yl)phenoxypropyl]trimethylammonium tetrafluoroborate 7a

Following procedure C using 4, aniline, and indene, a pale greenish solid was obtained in 60% yield. Mp 220–222 °C. <sup>1</sup>H NMR (300 MHz, acetonitrile-*d*<sub>3</sub>): 2.24–2.34 (m, 2H), 3.09 (s, 9H), 3.47–3.59 (m, 2H), 4.21 (t, 2H, *J*=5.7 Hz), 4.36 (s, 2H), 7.19 (d, 2H, *J*=8.7 Hz), 7.71–7.80 (m, 2H), 7.88 (dd, 1H, *J*<sub>1</sub>=3.4 Hz, *J*<sub>2</sub>=8.2 Hz), 8.00–8.09 (m, 3H), 8.14 (t, 1H, *J*=8.3 Hz), 8.75–8.78 (m, 1H), 8.83 (d, 1H, *J*=8.5 Hz), 9.09 (d, 1H, *J*=8.7 Hz). <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): 22.5, 38.6, 52.6 (t, *J*=4.0 Hz), 63.5, 64.6, 115.0, 121.2, 122.5, 123.6, 124.5, 125.4, 125.8, 128.0, 129.0, 131.2, 131.3, 133.2, 134.9, 137.6, 138.7, 147.8, 150.9, 153.4, 161.1. HRMS (FAB) [C<sub>28</sub>H<sub>29</sub>N<sub>2</sub>O][BF<sub>4</sub>]: calculated 409.2279, found: 409.2265 (C<sup>+</sup>).

##### 4.4.2. {3-[4-(2-Methyl-7H-indeno[2,1-c]quinolin-6-yl)phenoxypropyl]trimethylammonium tetrafluoroborate 7b

Following procedure C using 4, 4-methylaniline, and indene, a yellow solid was obtained in 62% yield. Mp 208–210 °C. <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>): 2.36–2.52 (m, 2H), 2.78 (s, 3H), 3.25 (s, 9H), 3.58–3.74 (m, 2H), 4.32 (t, 2H, *J*=5.7 Hz), 4.37 (s, 2H), 7.34 (d, 2H, *J*=8.6 Hz), 7.69–7.79 (m, 2H), 7.84–7.82 (m, 1H), 8.01 (m, 3H), 8.26 (d, 1H, *J*=8.7 Hz), 8.82 (d, 1H, *J*=8.7 Hz), 8.89 (s, 1H). <sup>13</sup>C NMR (75 MHz, acetonitrile-*d*<sub>3</sub>): 20.6, 22.5, 38.5, 52.6 (t, *J*=4.0 Hz), 63.5, 64.6, 115.0, 120.6, 122.7, 123.2, 123.4, 125.4, 126.1, 128.0, 131.2, 135.3, 137.0, 137.6, 140.2, 147.7, 149.8, 153.0, 161.1. HRMS (FAB) [C<sub>29</sub>H<sub>31</sub>N<sub>2</sub>O][BF<sub>4</sub>]: calculated 423.2436, found: 423.2436 (C<sup>+</sup>).

##### 4.4.3. {3-[4-(2-Methoxy-7H-indeno[2,1-c]quinolin-6-yl)phenoxypropyl]trimethylammonium tetrafluoroborate 7c

Following procedure C using 4, 4-methoxyaniline, and indene, a yellow solid was obtained in 60% yield. Mp 198–200 °C. <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>): 2.42–2.61 (m, 2H), 3.51 (s, 9H), 3.84–3.95 (m, 2H), 4.18 (s, 3H), 4.28–4.41 (m, 4H), 7.18 (d, 2H, *J*=8.7 Hz), 7.47–7.68 (m, 3H), 7.87 (d, 1H, *J*=7.2 Hz), 8.05–8.21 (m, 4H), 8.62 (d, 1H, *J*=7.2 Hz). <sup>13</sup>C NMR (75 MHz, acetonitrile-*d*<sub>3</sub>): 24.0, 38.3, 53.6 (t, *J*=4.0 Hz), 56.1, 64.9, 65.7, 102.8, 115.3, 122.5, 125.1, 125.2, 126.0, 128.3, 129.4, 131.0, 131.3, 132.4, 135.4, 140.7, 143.1, 146.2, 146.3, 152.5, 159.3, 160.3. HRMS (FAB) [C<sub>29</sub>H<sub>31</sub>N<sub>2</sub>O<sub>2</sub>][BF<sub>4</sub>]: calculated 439.2385, found: 439.2375 (C<sup>+</sup>).

##### 4.4.4. {3-[4-(2-Chloro-7H-indeno[2,1-c]quinolin-6-yl)phenoxypropyl]trimethylammonium tetrafluoroborate 7d

Following procedure C using 4, 4-chloroaniline, and indene, a yellow solid was obtained in 57% yield. Mp 224–226 °C. <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>): 2.30–2.51 (m, 2H), 3.25 (s, 9H), 3.59–3.73 (m, 2H), 4.24–4.35 (m, 4H), 7.28 (d, 2H, *J*=8.7 Hz), 7.64–7.72 (m, 2H), 7.82 (dd, 1H,

*J*<sub>1</sub>=2.0 Hz, *J*<sub>2</sub>=6.4 Hz), 7.99 (d, 2H, *J*=8.7 Hz), 8.27 (d, 2H, *J*=8.9 Hz), 8.64 (d, 1H, *J*=8.2 Hz), 8.96 (s, 1H). <sup>13</sup>C NMR (75 MHz, acetonitrile-*d*<sub>3</sub>): 22.5, 38.4, 52.6 (t, *J*=4.0 Hz), 63.5, 64.5, 114.8, 123.2, 125.1, 125.3, 125.4, 127.8, 130.8, 131.1, 132.4, 133.8, 135.8, 137.6, 139.4, 147.1, 150.6, 152.1, 160.8. HRMS (FAB) [C<sub>29</sub>H<sub>28</sub>N<sub>2</sub>OCl][BF<sub>4</sub>]: calculated 443.1890, found: 443.1892 (C<sup>+</sup>).

##### 4.4.5. {3-[4-(2-Bromo-7H-indeno[2,1-c]quinolin-6-yl)phenoxypropyl]trimethylammonium tetrafluoroborate 7e

Following procedure C using 4, 4-bromoaniline, and indene, a yellow solid was obtained in 56% yield. Mp 258–260 °C. <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>): 2.56–2.63 (m, 2H), 3.43 (s, 9H), 3.85–3.93 (m, 2H), 4.36 (t, 2H, *J*=5.7 Hz), 4.37 (s, 2H), 7.28 (d, 2H, *J*=8.7 Hz), 7.64–7.72 (m, 2H), 7.82 (dd, 1H, *J*<sub>1</sub>=2.0 Hz, *J*<sub>2</sub>=6.4 Hz), 7.99 (d, 2H, *J*=8.6 Hz), 8.27 (d, 2H, *J*=8.9 Hz), 8.64 (d, 1H, *J*=8.2 Hz), 8.96 (s, 1H). <sup>13</sup>C NMR (75 MHz, acetonitrile-*d*<sub>3</sub>): 23.8, 38.6, 53.8 (t, *J*=4.0 Hz), 64.9, 66.2, 115.8, 122.0, 125.0, 125.6, 126.4, 126.9, 128.8, 129.7, 129.9, 130.8, 131.8, 134.6, 136.6, 139.5, 144.2, 147.1, 148.4, 155.2, 161.1. HRMS (FAB) [C<sub>29</sub>H<sub>28</sub>N<sub>2</sub>OBr][BF<sub>4</sub>]: calculated 487.1385, found: 487.1382 (C<sup>+</sup>).

##### 4.4.6. {3-[4-(2-Nitro-7H-indeno[2,1-c]quinolin-6-yl)phenoxypropyl]trimethylammonium tetrafluoroborate 7f

Following procedure C using 4, 4-nitroaniline, and indene, a yellow solid was obtained in 50% yield. Mp 258–260 °C. <sup>1</sup>H NMR (300 MHz, methanol-*d*<sub>4</sub>): 2.36–2.50 (m, 2H), 3.27 (s, 9H), 3.64–3.75 (m, 2H), 4.35 (t, 2H, *J*=5.6 Hz), 4.50 (s, 2H), 7.38 (d, 2H, *J*=8.6 Hz), 7.76–7.86 (m, 2H), 7.89–7.99 (m, 1H), 8.14 (d, 2H, *J*=8.6 Hz), 8.57 (d, 1H, *J*=9.4 Hz), 8.72–8.80 (m, 1H), 8.86 (d, 1H, *J*=9.4 Hz), 9.89 (s, 1H). <sup>13</sup>C NMR (75 MHz, methanol-*d*<sub>4</sub>): 22.3, 53.7 (t, *J*=4.0 Hz), 65.4, 66.2, 116.2, 121.8, 123.1, 125.5, 126.1, 126.8, 127.2, 128.1, 128.7, 129.4, 132.1, 132.6, 137.7, 139.3, 146.6, 147.1, 148.5, 157.4, 162.6. HRMS (FAB) [C<sub>29</sub>H<sub>28</sub>N<sub>3</sub>O<sub>3</sub>][BF<sub>4</sub>]: calculated 454.2130, found: 454.2135 (C<sup>+</sup>).

##### 4.4.7. {3-[4-(2-Fluoro-7H-indeno[2,1-c]quinolin-6-yl)phenoxypropyl]trimethylammonium tetrafluoroborate 7g

Following procedure C using 4, 4-fluoroaniline, and indene, a brown solid was obtained in 62% yield. Mp 218–220 °C. <sup>1</sup>H NMR (300 MHz, acetonitrile-*d*<sub>3</sub>): 2.25–2.41 (m, 2H), 3.14 (s, 9H), 3.49–3.63 (m, 2H), 4.27 (t, 2H, *J*=5.7 Hz), 4.37 (s, 2H), 7.28 (d, 2H, *J*=8.7 Hz), 7.69–7.80 (m, 2H), 7.84–7.91 (m, 1H), 7.97 (d, 1H, *J*=8.6 Hz), 8.01 (d, 2H, *J*=8.8 Hz), 8.42 (d, 1H, *J*=5.4 Hz), 8.67 (m, 2H). <sup>13</sup>C NMR (75 MHz, acetone-*d*<sub>6</sub>): 23.7, 38.4, 53.8 (t, *J*=4.0 Hz), 64.8, 65.9, 109.7, 116.3, 123.3, 123.7, 124.5, 125.7, 126.3, 126.6, 126.8, 129.2, 132.2, 132.4, 136.8, 138.4, 138.7, 148.4, 152.7, 162.3 (d, *J*=250 Hz), 162.1. HRMS (FAB) [C<sub>29</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>F][BF<sub>4</sub>]: calculated 427.2185, found: 427.2191 (C<sup>+</sup>).

##### 4.4.8. {3-[4-(2-Chloro-7H-indeno[2,1-c]quinolin-6-yl)benzoxypyl]trimethylammonium tetrafluoroborate 8a

Following procedure C using 3, 4-chloroaniline, and indene, a yellow solid was obtained in 60% yield. Mp

>260 °C. <sup>1</sup>H NMR (300 MHz, acetonitrile-*d*<sub>3</sub>): 2.20–2.41 (m, 2H), 3.12 (s, 9H), 3.43–3.56 (m, 2H), 4.09 (s, 2H), 4.45 (t, 2H, *J*=5.8 Hz), 7.53–7.56 (m, 2H), 7.68 (d, 1H, *J*=8.5 Hz), 7.78 (d, 1H, *J*=8.5 Hz), 8.02 (d, 2H, *J*=8.3 Hz), 8.15 (d, 1H, *J*=8.7 Hz), 8.23 (d, 2H, *J*=8.3 Hz), 8.41 (d, 1H, *J*=8.7 Hz), 8.68 (s, 1H). <sup>13</sup>C NMR (75 MHz, acetonitrile-*d*<sub>3</sub>): 22.0, 38.4, 52.6 (t, *J*=4.0 Hz), 61.5, 63.5, 122.4, 123.8, 124.1, 125.0, 127.3, 128.8, 128.9, 129.4, 129.9, 129.9, 130.5, 132.5, 135.4, 138.7, 142.9, 144.9, 145.1, 154.3, 165.9. HRMS (FAB) [C<sub>29</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>Cl][BF<sub>4</sub>]: calculated 427.2185, found: 427.2191 (C<sup>+</sup>).

#### 4.4.9. {3-[4-(2-Methyl-7H-indeno[2,1-*c*]quinolin-6-yl)-benzoxypyrrol]trimethylammonium tetrafluoroborate 8b

Following procedure C using 3, 4-methylaniline, and indene, a yellow solid was obtained in 59% yield. Mp 200–202 °C. <sup>1</sup>H NMR (300 MHz, acetonitrile-*d*<sub>3</sub>): 2.35–2.48 (m, 2H), 2.81 (s, 3H), 3.21 (s, 9H), 3.58–3.67 (m, 2H), 4.36 (s, 2H), 4.54 (t, 2H, *J*=5.8 Hz), 7.74–7.83 (m, 2H), 7.89 (d, 1H, *J*=8.7 Hz), 8.07 (d, 1H, *J*=8.4 Hz), 8.17 (d, 2H, *J*=8.3 Hz), 8.32 (d, 1H, *J*=8.7 Hz), 8.42 (d, 2H, *J*=8.3 Hz), 8.89 (d, 1H, *J*=8.4 Hz), 8.97 (s, 1H). <sup>13</sup>C NMR (75 MHz, acetonitrile-*d*<sub>3</sub>): 20.7, 22.1, 52.6 (t, *J*=4.0 Hz), 61.3, 63.5, 122.4, 123.3, 123.5, 125.0, 125.1, 128.4, 129.1, 129.5, 129.7, 131.0, 133.2, 134.6, 135.0, 139.0, 141.0, 142.2, 149.7, 152.0, 153.5, 165.8. HRMS (FAB) [C<sub>30</sub>H<sub>31</sub>N<sub>2</sub>O<sub>2</sub>][BF<sub>4</sub>]: calculated 471.1839, found: 471.1835 (C<sup>+</sup>).

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